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CLINICAL EXPERIENCE WITH CHLOROTHIAZIDE (DIURIL), WITH PARTICULAR EMPHASIS ON UNTOWARD RESPONSES A REPORT OF 121 CASES STUDIED OVER A 15 MONTH PERIOD

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Chlorothiazide is the generic name of a potent, orally effective, nonmercurial, diuretic agent, a substituted benzothiadiazine compound with a free sulfonamide group, which was synthesized in 1957 by Novello and Sprague[13]. It is designated chemically as 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1, 1-dioxide and has recently (1958) been available in the United States as Diuril.* Preclinical studies (Beyer[2]) with this new sulfonamide demonstrated its ability to promote the excretion of sodium and chloride (also to a lesser degree potassium and bicarbonate) and led to its designation as a *saluretic* agent. The exact mechanism by which this drug alters ion transport in the kidney has not been completely established. It would appear that its mode of action at least is different from that of other presently known diuretics (Laragh, Heinemann and Demertini[11]), with its effects resembling the organomercurials and yet reminiscent of the classic carbonic anhydrase inhibitors (Beyer[3]). Currently, the pharmacologic effects (Ford, Moyer and Spurr[6]), potency (Ford *et al.*[8]) and advantages (Ford *et al.*[7]) of chlorothiazide in man are well recognized, as well as its clinical effectiveness in initiating diuresis and in maintaining the edema-free state (Bayliss *et al.*[1], Cornish[4], Laragh, Heinemann and Demertini[11], Schreiner and Bloomer[15],

*The chlorothiazide (Diuril) used in this study was supplied through the kindness of John R. Beem, M.D. of Merck Sharp and Dohme, Division of Merck and Co., Inc., West Point, Pa.

Slater and Nabarro[16]) and in the treatment of hypertension (Freis *et al.*[9], Hollander and Wilkins[10]) and of the toxemias of pregnancy (Finnerty, Buchholz and Tuckman[5]).

This study was begun in April, 1957, as a clinical evaluation of a new diuretic drug supplied to us for investigational use. Our purpose was to obtain a broad working experience with this compound and to assess its role in clinical problems under conditions similar to those commonly encountered in general medical practice. Such clinical information should be of practical importance to physicians, since this drug has not been generally available long enough for the average practitioner to have a comparable experience. At first only hospitalized patients carefully controlled and under daily observation were selected, but subsequently as our experience increased and the drug was found to be well tolerated, nonhospitalized patients were included. Data on 121 of these patients (57 women and 64 men) from the medical and cardiovascular services of the Pennsylvania Hospital form the basis of this report. Their ages ranged from 17 to 90 with 88% of the patients between 40 and 80 years. The etiologic diagnoses with the number of patients in each category are recorded in Table 1. The predominance of elderly patients with cardiac disease is a reflection of our objective and of the availability of a large number of such pa-

TABLE 1.—THE DIAGNOSES AND CLINICAL RESULTS OF CHLOROTHIAZIDE THERAPY IN 121 PATIENTS

Diagnoses	*No. of Patients*	*Results*			
		Excellent	*Good*	*Fair*	*Poor*
Cardiac disease	102	30	42	21	9
Arteriosclerotic	51	16	20	11	4
Hypertensive	25	5	13	5	2
Rheumatic	14	6	5	2	1
Luetic	4	1	1	2	–
Cor pulmonale	7	2	2	1	2
Viral myocarditis	1	–	1	–	–
Hepatic cirrhosis	9	1	2	3	3
Renal disease	6	1	2	–	3
Chronic glomerulonephritis	2	–	1	–	1
Nephrosis	1	1	–	–	–
Kimmelstiel-Wilson disease	3	–	1	–	2
Others	4	–	3	1	–
Premenstrual edema	2	–	2	–	–
Peritoneal carcinomatosis	2	–	1	1	–
Total	121	32	49	25	15

tients requiring diuretic therapy in our adult Heart Clinic.

Method. The patients were appraised prior to chlorothiazide therapy to insure that a diuretic agent was necessary and that all other therapeutic measures applicable in each individual case were being adequately and correctly employed, that a low salt diet was being enforced, and that digitalization, where indicated, was complete. If patients were already receiving diuretic drugs (for example, organomercurials) the latter were discontinued and the patient placed under observation without such therapy to determine the actual need for these agents. Placebo tablets were also given initially or intermittently substituted during the chlorothiazide trials.

When it was clear that a diuretic drug was indicated, chlorothiazide was given orally in divided doses varying from 0.5 to 1.5 (rarely 2.0) gm. daily or intermittently several days each week. Increases in dosage were conservative and gradual and only if the response or control was not satisfactory. For long-term outpatient treatment dosages usually below 1.0 gm. daily on an intermittent schedule were attempted. The majority of patients were on a restricted sodium intake, varying from 0.25 to 1.0 gm. sodium diet daily in the hospitalized patients to "no added salt" diet in the outpatients. Supplements of potassium salts were not routinely employed, but daily orange juice was prescribed in the diet of most patients. The body weight, urinary output, physical findings and subjective results were carefully followed. Complete blood counts, urinalyses, electrocardiograms, chest roentgenograms, phenolsulfonphthalein excretion tests and determinations of blood urea nitrogen and serum and urinary electrolytes were performed. The latter were regularly observed in the earlier portion of this study with hospitalized patients, but subsequently with outpatients only intermittently as a "spot check" determination or when clinical indications or difficulties arose. The nonhospitalized patients were followed at weekly intervals during the first few months of outpatient management and those not able to return weekly were not included in the study. Those showing well-tolerated control and understanding of the program were subsequently followed at several weeks' (rather than weekly) intervals. The duration of individual follow-up varied from weeks to months. The longest period of continued therapy was 15 months in 8 patients.

Results. The over-all individual response in this series of 121 patients was classified by the attending physicians on a clinical basis and the results are summarized in Table 1. It is evident that in most of the patients, chlorothiazide was a very effective, oral diuretic agent. Continued long-term therapy was simple and practical in most patients over periods up to 15 months. Brief case reports will be presented, illustrating the beneficial effects and some of the problems encountered.

Case Reports. CASE 1.—J.H., a 47-year-old cleaning woman with arteriosclerotic heart disease was hospitalized (July, 1957) with severe congestive heart failure, for which the usual therapeutic measures were instituted. After base line studies, chlorothiazide 0.25 gm. was given twice daily by mouth with marked diuresis, weight loss, and clinical improvement. Serum and urine electrolytes were carefully followed (Fig. 1). Excellent edema control was maintained with the same daily dosage of chlorothiazide 5 days per week as an outpatient for 12 months with no untoward results and no further hospitalizations. She returned to work.

CASE 2.—A.D., a 51-year-old white man with rheumatic heart disease, atrial fibrillation, mitral insufficiency and stenosis, requiring digitalis, sodium restriction and mercurial injections at least twice weekly, developed a mercurial hypersensitivity skin reaction and was hospitalized in congestive failure. He was treated with bed rest, a restricted sodium diet and digitalis. A challenging, mercurial injection again produced a maculopapular skin eruption. Chlorothiazide 0.25 gm. three times daily was instituted (April, 1957) with dramatic diuresis and clinical improvement. He was maintained on chlorothiazide 0.25 gm. twice daily as an outpatient for 15 months with excellent control of edema, no untoward reactions and no further hospitalizations.

The divided total dosage taken at 6- to 12-hour intervals appeared more effective than the whole dose taken once in the 24-hour period. Diuretic unresponsiveness was not a problem with continued, daily use. Though uninterrupted therapy with small daily doses was effective and generally well toler-

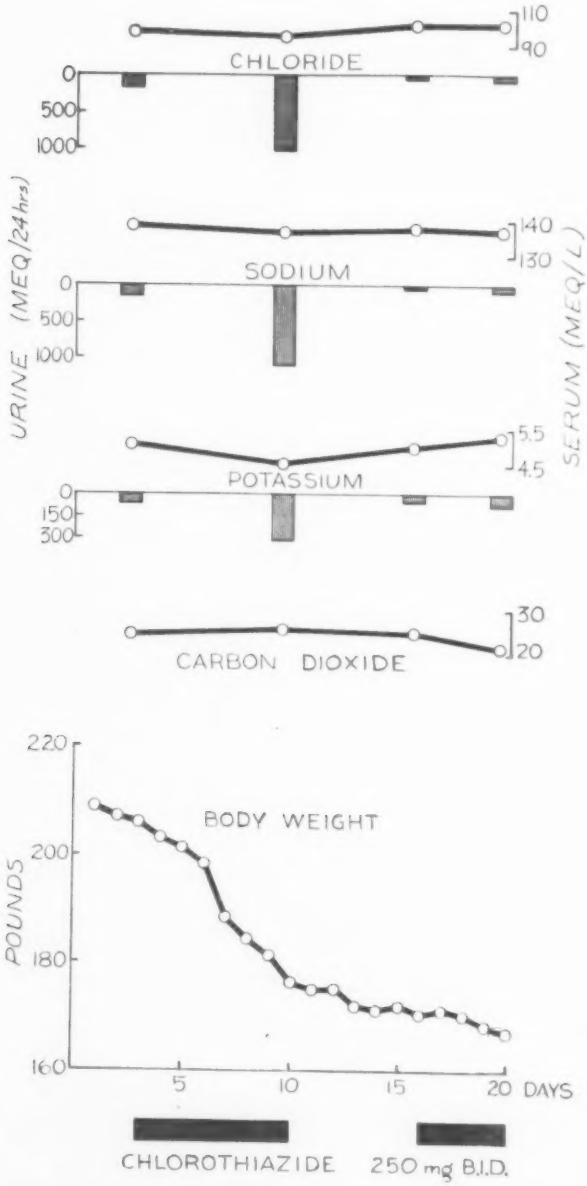

Fig. 1.—Chart of patient, J. H. (Case 1) with congestive heart failure, showing the effects of chlorothiazide therapy on body weight, urinary electrolyte excretion and serum electrolyte values.

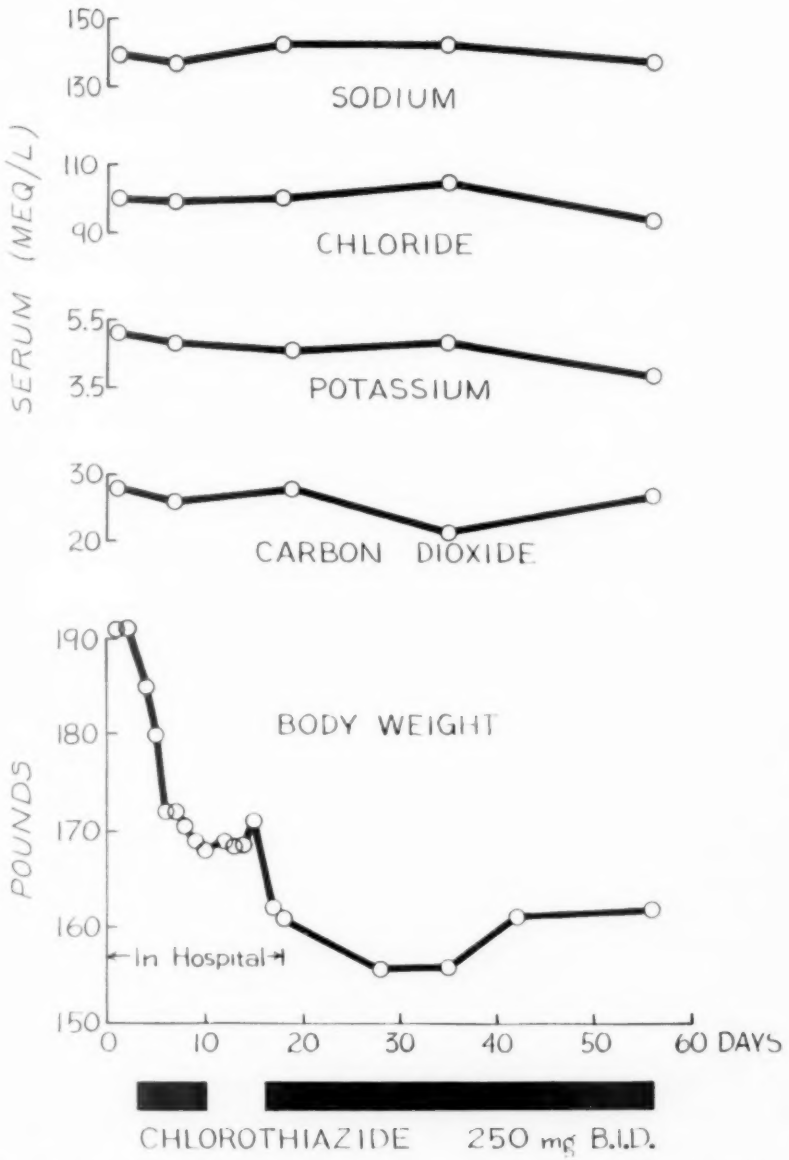

Fig. 2.—Chart of patient, L.D. (Case 3) with congestive heart failure, showing the effects of chlorothiazide therapy on body weight and serum electrolyte values in the hospital and subsequently in the outpatient clinic.

ated, intermittent administration was associated with less electrolyte difficulties when larger doses of the drug were necessary.

CASE 3.—L.D., a 53-year-old colored man with hypertensive cardiovascular disease and old cerebral vascular accident, taking digitalis, low sodium diet and periodically mercurial injections, entered the hospital (October, 1957) in severe congestive failure with paroxysmal nocturnal dyspnea and 4 plus pitting edema to the groins. After base line studies and observations and the usual cardiac therapy, he received chlorothiazide 0.25 gm. twice daily with dramatic results (Fig. 2). He was later maintained on this daily schedule as an outpatient for a total of almost 2 months with essentially no change in serum electrolyte values.

CASE 4.—H.A., a 67-year-old machinist with coronary heart disease and old myocardial infarction, taking a restricted sodium diet and digitalis daily, required mercurial injections once or twice weekly with resultant 6 to 8 pounds weight loss, weakness, lethargy, muscle cramps and unsatisfactory control of edema over a period of one year. During this time, there were two hospitalizations for severe congestive failure, necessitating thoracenteses. For 15 months (since April, 1957) the mercurials were replaced by chlorothiazide 0.5 gm. and 0.75 gm. alternately, 6 days per week with excellent control of edema. No further hospitalizations were required and no untoward reactions occurred.

As the drug was used over a greater period of time under different clinical circumstances, various untoward responses were witnessed. These will be considered in the remaining portion of this report.

ELECTROLYTE DISTURBANCES. A marked pharmacological (diuretic) response to the drug may result in fluid and electrolyte imbalance, such as the "low salt syndrome" or hyponatremia, hypochloremic alkalosis, and hypokalemia. These are obviously more likely to occur if a marked and rapid diuresis is injudiciously induced by too vigorous therapy. Often responsible for such a disturbing diuresis are over-zealous "shot-gun" measures, employing simultaneously a diuretic agent with thoracentesis, digitalization, low salt intake and bed rest. Less detrimental would be the reverse sequence of (temporarily) withholding the diuretic agent while the other measures are rationally instituted and their effects observed. Electrolyte difficulties are also apt to occur in patients with resistant edema maintained on a very restricted sodium intake with continuous (rather than intermittent) chlorothiazide treatment in large doses.

CASE 5. W.J., a 44-year-old colored man with arteriosclerotic heart disease, receiving a low-sodium diet, digitalis and occasional mercurial injections, developed severe congestive failure and was hospitalized. Initial studies showed serum sodium 138 mEq. per L., chlorides 103 mEq. per L., potassium 5.7 mEq. per L., CO_2-combining power 30 mEq. per L. and blood urea nitrogen 36 mg. per 100 ml. Chlorothiazide 0.5 mg. twice daily was then begun. In 5 days the patient lost 32 pounds and complained of weakness and anorexia. Studies at this time revealed serum sodium 132 mEq. per L., chlorides 82 mEq. per L., potassium 5.1 mEq. per L., CO_2-combining power 38 mEq. per L. and blood urea nitrogen 15 mg. per 100 ml. (hypochloremic alkalosis).

CASE 6. G.N., a 49-year-old man with cirrhosis of the liver and previous hospitalizations for multiple paracenteses and thoracenteses, was readmitted in respiratory distress with nearly complete right hydrothorax, marked ascites and 4 plus pitting edema of the legs. Initial studies revealed serum sodium 130 mEq. per L., chlorides 97 mEq. per L., potassium 4.3 mEq. per L. and CO_2-combining power 24 mEq. per L. He was continued on a high-calorie, high-protein and low-sodium diet with vitamin supplements and started on chlorothiazide 0.25 gm. twice daily. During the first week, abdominal paracentesis and thoracentesis were performed and chlorothiazide was maintained. He became much worse with weakness, lethargy, hypotension (blood pressure 80/50 mm. Hg) and oliguria. Repeat electrolyte studies now showed serum sodium 114 mEq. per L., chlorides 86 mEq. per L., potassium 6.6 mEq. per L., CO_2-combining power 20 mEq. per L. and blood urea nitrogen 38 mg. per 100 ml. He was given hypertonic sodium chloride and adrenocortical steroids

and chlorothiazide was discontinued. He improved clinically with a return to the previous blood pressure level of 120/70 mm. Hg and increased urinary output. Electrolyte studies then showed serum sodium 120 mEq. per L., chlorides 94 mEq. per L. and potassium 4.8 mEq. per L. (low salt syndrome or hyponatremia as a result of salt depletion by paracentesis and thoracentesis in combination with diuretic therapy and low sodium intake).

CASE 7. H.Q., a 32-year-old white woman with rheumatic heart disease, requiring digitalis, sodium restriction and occasional mercurial injections, was hospitalized in congestive heart failure. She was given bed rest, low sodium diet, increased digitalis and mercurial injections during the first week with a loss of 9 lbs. Serum electrolytes were rechecked and revealed serum sodium 140 mEq. per L., chlorides 94 mEq. per L., potassium 4.2 mEq. per L., CO_2-combining power 32 mEq. per L. and blood urea nitrogen 9 mg. per 100 ml. Chlorothiazide 0.5 gm. twice daily was then started. One week later, there had been an 8-lb. weight loss but she felt worse and complained of weakness, anorexia and nausea. Electrolyte studies now showed serum sodium 125 mEq. per L., chlorides 86 mEq. per L. and potassium 4.6 mEq. per L. Chlorothiazide was discontinued. Despite therapeutic attempts with added and later restricted sodium chloride, limited fluid intake, aminophylline, ammonium chloride, reinstituted mercurials, chlorothiazide and adrenocortical steroids, the patient failed progressively. Serum studies prior to death showed sodium 113 mEq. per L., chlorides 77 mEq. per L., potassium 7.6 mEq. per L., CO_2-combining power 17 mEq. per L. and blood urea nitrogen 50 mg. per 100 ml.

HYPOKALEMIA. Increased excretion of potassium with resultant hypokalemia has been observed to be an important untoward response to chlorothiazide with possible serious consequences, occurring even in the absence of marked diuresis or excessive dosages of the drug. An example of induced hypokalemia without a marked diuresis was encountered in a patient complaining of muscular weakness.

CASE 8. W.G., a 46-year-old hypertensive, nonedematous, white man, maintained a low-sodium intake and had been treated with Rauwolfia and mecamylamine for several months with only fair results. Chlorothiazide 0.25 gm. three times daily was added to this regimen. After a period of 3 weeks with a 10-lb. weight loss, he complained of *severe* generalized muscular weakness, The serum potassium was found to be 1.8 mEq. per L. His clinical state responded dramatically to potassium salts administered orally. The day after the potassium therapy was started and with some clinical improvement already noted, the serum potassium was still only 2.3 mEq. per L. The serum sodium was 147 mEq. per L., chlorides 96 mEq. per L., calcium 9.4 mg. per 100 ml. and CO_2-combining power 32.9 mEq. per L. at the time of the second determination.

Hypokalemia in turn may potentiate the toxic effects of digitalis on the heart (Lown *et al.*[12]). Moreover, in patients with serious liver disease, potassium depletion has also been considered a possible precipitating factor of hepatic coma (Read *et al.*[14]).

CASE 9. E.H., a 64-year-old white man with hypertensive and arteriosclerotic heart disease and hepatic cirrhosis continued to develop increasing edema despite a low-salt diet, digitoxin 0.1 mg. daily and parenteral mercurial therapy. Chlorothiazide 0.5 gm. was added twice daily for 2 weeks and 1.0 gm. twice daily for one week with a 20 lb. weight loss during this period. He developed marked weakness, palpitation and syncopal attacks, for which he was referred to the hospital by his family physician. While in the Emergency Room, he suddenly slumped forward, gave a few gasps and became cyanotic. The heart beat could not be heard. The intern pounded on the patient's chest several times and administered oxygen by mask and bag compression with return of heart sounds. Subsequent electrocardiogram (Fig. 3*A*) showed atrio-ventricular dissociation with occasional ventricular capture and frequent premature ectopic ventricular contractions consistent with digitalis intoxication. Digitalis was discontinued and he was given 80 mEq. of potassium by intravenous drip and quinidine by mouth with return to normal sinus rhythm (Fig. 3*B*) by the following day.

CASE 10. H.W., a 55-year-old white man with severe hypertensive cardiovascular disease and previous bilateral thoraco-lumbar sympathectomy had been maintained on a sodium-restricted diet, Rauwolfia, mecamylamine and digitalis folia (0.1 gm. daily) for over a year. To this regimen was added chlorothiazide 0.25 gm. twice daily. Two

weeks later, he developed frequent premature contractions with periods of coupled rhythm. Chlorothiazide was stopped and the arrhythmia ceased. It was again administered in the same dosage and after a few days the premature contractions recurred. Chlorothiazide was again discontinued and for 3 months no irregularity was noted by the patient (who was very conscious of it) or by his physicians.

CASE 11. H.C., a 56-year-old white man with chronic alcoholism and cirrhosis of the liver was hospitalized because of weakness and mental confusion. Ascites and hepatosplenomegaly were present. He was given a low-protein and low-sodium diet, intravenous infusions of glucose, vitamin supplements, oral neomycin, glutamic acid, and chlorothiazide 0.5 gm. twice daily. He developed tremors and "liver-flap." There had been no marked diuresis, but the serum potassium was 2.8 mEq. per L. The chlorothiazide was stopped and oral potassium chloride 8 gm. daily was added to the therapy with gradual improvement of the sensorium and disappearance of tremors. The serum potassium was then 3.6 mEq. per L.

POTENTIATION OF ANTIHYPERTENSIVE DRUGS. Chlorothiazide will enhance the the effectiveness of ganglionic blocking agents in the treatment of hypertensive patients (Tapia *et al.*[17]). Excessive hypotensive response with possible serious sequelae may occur when this drug is added to a therapeutic regimen of antihypertensive agents unless the dosage of the latter is concomitantly reduced.

CASE 12. L.B., a 53-year-old attorney with hypertensive and arteriosclerotic cardiovascular disease (B. P. 210/110 mm. Hg) and angina of effort, taking a sodium-restricted diet, mecamylamine 2.5 mg. twice daily to 7.5 mg. three times daily and nitroglycerin as needed, was given, in addition, chlorothiazide 0.5 gm. twice daily. A week later, upon arising from bed to urinate, he fell momentarily in a faint to the bathroom floor. On admission to the hospital his blood pressure was 180/100 mm. Hg (recumbent) and 100/70 mm. Hg (standing). Serial electrocardiograms showed the changes of a recent posterior myocardial infarction.

Fig. 3.—Electrocardiogram (Lead V2) of patient, E.H. (Case 9): (*A*)Taken in the Emergency Room, showing A–V dissociation with occasional ventricular capture, and frequent premature ectopic ventricular contractions consistent with digitalis intoxication; (*B*) Taken the following day after intravenous potassium chloride and other therapy, showing a return to normal sinus rhythm with occasional premature ventricular contractions.

The reverse of this was also observed in a hypertensive patient receiving reserpine and mecamylamine in whom chlorothiazide was discontinued and sodium chloride given because of the development of salt depletion syndrome.

CASE 13. E.L., a 53-year-old colored woman with severe, uncontrolled hypertension (B.P. 280/160 mm. Hg) was rehospitalized in early heart failure. Initial electrolyte studies were within normal limits

with serum sodium 140 mEq. per L., chlorides 97 mEq. per L., potassium 4.1 mEq. per L. and blood urea nitrogen 14 mg. per 100 ml. She was given digitalis and a 200-mg. sodium diet, reserpine 0.25 mg. daily, mecamylamine 5 mg. three times daily and then, in addition, chlorothiazide 0.25 gm. twice daily with marked reduction in blood pressure (even to 110/80 mm. Hg standing). However, she was generally weak, mentally disturbed and uncooperative, refusing to eat. On the eighth day the serum sodium was 129 mEq. per L., chlorides 77 mEq. per L., potassium 3.2 mEq. per L. and blood urea nitrogen 28 mg. per 100 ml. Chlorothiazide was immediately discontinued, sodium chloride given and the other drugs maintained. The following day her blood pressure was 300+/180 mm. Hg (supine and restrained) and her behavior psychotic, requiring sedation and higher doses of the mecamylamine to lower her blood pressure again.

CHANGES IN URIC ACID. The development of hyperuricemia in 6 out of 8 patients taking chlorothiazide (2.0 gm. daily) in the treatment of edema was reported (Laragh, Heinemann and Demertini.[11]). An increase in the serum uric acid level was also noted (Cornish[4]) in a patient with gout and arteriosclerotic heart disease receiving this drug (0.5 gm. daily). We studied this effect of chlorothiazide (1.0 gm. daily) in two student nurses with premenstrual edema and 3 patients with gouty arthritis. Our preliminary results are summarized in Table 2. The gouty patient not taking probenecid showed (after 6 days of 1.0 gm. chlorothiazide daily) a marked but asymptomatic rise in serum uric acid. In the 2 patients with gout taking probenecid concomitantly with the chlorothiazide this rise did not occur. Instead, a fall in the serum uric acid resulted. Determinations of 24-hour urinary excretion of uric acid were also performed in these patients. Unexpectedly, a decrease in the urinary excretion of uric acid was noted in the latter 2 subjects. Because of the possibility of incomplete urine collections, these results are being withheld pending further investigation. The number of patients is too small for any conclusion to be reached, though therapeutic and physiologic implications are provoked. At present, a practical point to be derived is one of caution in interpreting the hyperuricemia in patients taking chlorothiazide and suspected of having gout or toxemia of pregnancy.

TABLE 2.—EFFECT OF CHLOROTHIAZIDE ON SERUM URIC ACID

	Control Values		*After 1 gm. Daily for 6 Days**	
Diagnoses	*Uric Acid (mg./100 ml.)*	*Urea (mg./100 ml.)*	*Uric Acid (mg./100 ml.)*	*Urea (mg./100 ml.)*
Premenstrual edema	3.1	12	3.1	10
Premenstrual edema Diabetes mellitus	2.9	21	3.6	31
Gout (no probenecid)	4.7	—	12.1	18
Gout (with probenecid)	9.4	25	6.2	23
Gout (with probenecid)	7.1	—	4.7	25

*During this period no acute attacks of arthritis developed.

OTHER SIDE REACTIONS. Weakness, fatigability, lethargy and mental depression; nausea, vomiting, epigastric distress and diarrhea; malaise and anorexia; paresthesias; skin rashes; muscle cramps, flushing and lightheadedness have been noted in this

and other clinical studies as occasional, uncommon, or rare side effects.

CASE 14. W.H., a 79-year-old colored man with arteriosclerotic heart disease, complained of marked weakness and lethargy following initiation of chlorothiazide therapy. Serum electrolytes were repeated and were found again to be within normal limits. After the drug was discontinued, the symptoms disappeared.

TOXIC EFFECTS. Serious toxic reactions secondary to this drug have not been so stated in clinical reports to date.

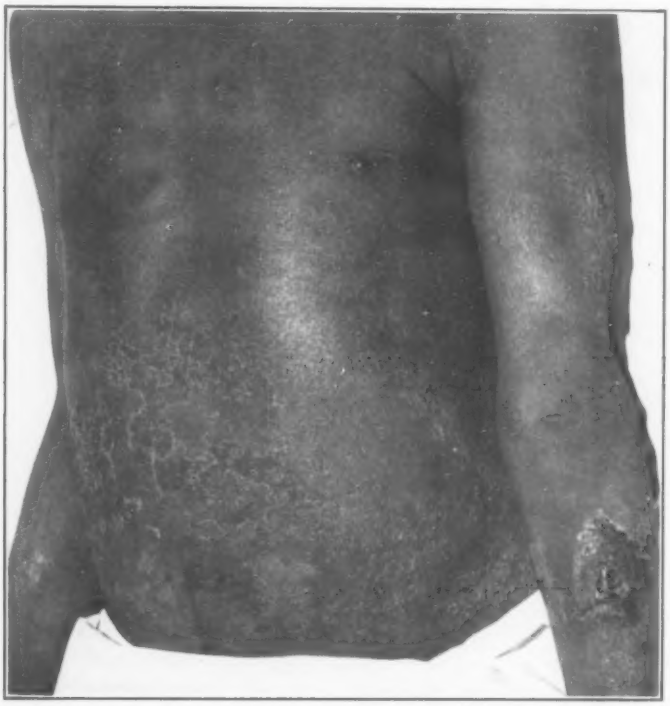

Fig. 4.—Photograph of patient, L.D. (Case 3) who developed pruritus, fever, exfoliative dermatitis, lymphadenopathy, splenomegaly, eosinophilia and shock with cerebrovascular insufficiency, while receiving chlorothiazide. The forearm areas of tissue slough are a complication of the intravenous infusions of norepinephrine.

CASE 3. (cont'd). L.D., a 53-year-old colored man, after approximately 2 months of continuous chlorothiazide therapy (Fig. 2) developed pruritus, fever, exfoliative dermatitis, lymphadenopathy, splenomegaly, eosinophilia, and shock with cerebrovascular insufficiency, neurological changes and unresponsiveness. Vigorous supportive measures were necessary, including prolonged administration of continuous intravenous infusions of norepinephrine and adrenocortical steroids to maintain an adequate systemic arterial pressure. A complication of this intravenous therapy (local tissue slough), a recurrence of the skin reactions after discontinuing the corticoids (necessitating their re-institution) and a protracted convalescent period resulted. Fortunately, recovery occurred (Fig. 4).

However, an addendum (Laragh, Heinemann and Demertini[11]) described a patient with chronic congestive failure, receiving a number of drugs in addition to chlorothiazide, who developed a decreased urinary output and blood urea nitrogen values above 150 mg. per 100 ml. as a terminal event. At necropsy this patient showed non-

specific changes in the renal tubules with normal glomeruli.

Hematologic changes have not been reported, but a patient receiving chlorothiazide was recently studied at our hospital with blood and bone marrow findings suggestive of a drug toxicity.

CASE 15. H. G., a 54-year-old white woman with hypertensive cardiovascular disease and a previous admission for thrombophlebitis, was hospitalized with scattered ecchymoses, slurred speech and a right hemiplegia. She had been taking among other medications, chlorothiazide in doses of 0.5 to 1.0 gm. daily. Blood studies showed hemoglobin 12 gm.%, neutropenia and thrombocytopenia. Bone marrow aspiration disclosed granulocytic maturation arrest and increased numbers of young megakaryocytic forms and eosinophils. At necropsy the immediate cause of death was ascribed to cerebral and myocardial infarctions.

Discussion. The pharmacologic effects and clinical benefits of diuretics depend essentially on their ability to interfere with metabolic (biochemical) processes in the kidney and these agents (especially when injudiciously employed) may lead to electrolyte imbalances. In turn, electrolyte disturbances, brought about by vigorous diuretic therapy, rigid sodium restriction or disease processes may result in a failure to respond to diuretics. It must be accepted, however, that in advanced states of disease with impaired glomerular filtration and decreased sodium load to the renal tubules, despite maximal tubular interference by a potent drug, virtually all of the sodium presented may be re-absorbed and the anticipated diuresis may not occur.

It has been shown that chlorothiazide is capable of producing electrolyte alterations under various circumstances. This is more or less a potentiality of all effective diuretics, reflecting their pharmacologic action. However, the simplicity of administration and effectiveness of chlorothiazide may make such complications more likely. The usual adult daily dosage is 0.5 to 1.5 gm. by mouth given in divided doses at 12-hour intervals. Dosages greater than 2.0 gm. daily in general have no greater diuretic effect. Uninterrupted daily administration usually remains pharmacologically effective and may be tolerated. However, the smallest effective dose per day and per week (employing ideally an intermittent schedule) with its lessened biochemical alterations should be sought individually for each patient. Those requiring dosages greater than 1.0 gm. daily should be carefully followed, including periodic serum electrolyte determinations. Profound diuresis, multiple therapies and procedures, and complications of vomiting and diarrhea, should be avoided or taken into account if the diuretic must be administered. Therapeutic dosages not accompanied by an effective response should not be maintained, since the excretion of desirable electrolytes may be induced.

Certain patients appear to be more responsive to the kaliuretic effect of chlorothiazide than others. Perhaps under circumstances in which sodium is avidly retained or not readily available for excretion, as in rigid dietary sodium restriction, sodium depletion, and certain disease states; potassium or other cations rather than sodium may accompany the chloruresis and lead to the depletion of these ions. Careful clinical observation, periodic electrolyte determinations, and supplements of potassium salts or citrus fruit juices in the diet are recommended for patients receiving this drug over any prolonged period of time.

The enhancement of the hypotensive effect of various anti-hypertensive drugs (and surgical splanchnicectomy) has been attributed to the natriuretic-diuretic effect of chlorothiazide with

reduction of total body sodium and fluid (Tapia *et al.*[17]). A direct hypotensive effect of the drug in addition has been also suggested (Hollander and Wilkins[10]). In any event, a reduction in dosage of anti-hypertensive drugs, especially the ganglionic-blocking agents, by one-half or more, when chlorothiazide is added to the therapeutic program, is advised in order to avoid an excessive fall in blood pressure. It is to be recalled that this drug is a sulfonamide and it is probable that a broader experience with it will reveal some sensitivities and allergic responses characteristic of this group of compounds.

Summary. Our clinical experience with chlorothiazide as a diuretic and antihypertensive agent over a 15-month period has been described. Excellent or good results were obtained in most of the 121 patients studied. Serum electrolyte disturbances were encountered in the form of the "low salt syndrome," hypochloremic alkalosis and hypokalemia, in a number of patients. The latter finding appeared unexpectedly in certain individuals even in the absence of a marked diuresis or large doses of the drug, suggesting a selective increase in potassium excretion in some patients. Excessive hypotensive effect may occur when chlorothiazide is used concomitantly with anti-hypertensive drugs, especially the ganglionic blocking agents. A nearly fatal allergic (drug) reaction was observed, as well as several minor side effects and one possible hematologic toxic reaction with neutropenia and thrombocytopenia.

Electrolyte disturbances may be lessened by employing the lowest daily and weekly effective dosage schedule and by a short rest period from the drug every few days. Careful clinical and laboratory observations are indicated in all patients receiving chlorothiazide, but especially in those who are also taking digitalis or anti-hypertensive drugs or who have serious liver disease. Supplements of potassium salts in the form of potassium chloride or citrus fruit juices are desirable in most patients.

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SUMMARIO IN INTERLINGUA

Experientia Clinic Con Chlorothiazido (Diuril), Con Attention Special Prestate Al Responsas Adverse

Reporto De 121 Casos, Studiate In Le Curso De Un Periodo De 15 Menses

Es describite nostre experientias clinic con le uso de chlorothiazido como agente diuretic e antihypertensive durante un periodo de 15 menses. In le majoritate del 121 patientes studiate, le resultatos obtenite esseva excellente o bon. Disturbationes de electrolyto seral esseva incontrate in le forma del "syndrome del restriction de natrium," de alcalosis hypochloremic, e de hypokalemia in un certe numero del patientes. Hypokalemia se manifestava inexpectatemente in certe individuos mesmo in le absentia de marcate grados de diurese o de grande doses del droga. Isto suggere le presentia de un augmento selective del excretion de kalium in certe patientes. Un excesso del effecto hypotensive pote occurrer quando chlorothiazido es usate in concomitantia con drogas anti-hypertensive, specialmente le agentes de blocage ganglionic. Un caso de quasi mortal reaction allergic al droga esseva observate. Es a reportar etiam plure minor effectos lateral e possibilemente un caso de reaction toxic hematologic con neutropenia e thrombocytopenia.

Disturbationes de electrolyto seral pote esser reducite per usar le plus basse efficace plano de dosage diurne e septimanal e per interpolar breve periodos de abstention ab le droga a intervallos de alicun dies. Meticulose observationes clinic e laboratorial es indicate in omne patientes qui recipe chlorothiazido, sed specialmente in patientes qui etiam prende digitalis o drogas anti-hypertensive o qui ha un serie morbo hepatic. Supplementos de sales de kalium in le forma de chloruro de kalium o succos de citro es desirabile in le majoritate del patientes.

SUMMARIO IN INTERLINGUA

(See page 546 for original article)

Encephalopathia Associate Con Trichinosis: Tractamento Con ACTH E Cortisona

Reporto De Duo Casos

Es reportate duo casos de encephalopathia associate con trichinosis. In ambes, melioration rapide del symptomas sequeva le therapia a steroides. Es signalate le difficultate del diagnose in tal casos. Es proponite que le morbo es prendite in consideration in le diagnose differential de obscur acute disordines neurologic.

ENCEPHALOPATHY ASSOCIATED WITH TRICHINOSIS TREATMENT WITH ACTH AND CORTISONE REPORT OF TWO CASES

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and

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Trichinosis at times produces a bizarre pattern of central nervous system involvement presenting difficult problems in diagnosis. The rapid improvement in symptoms, and, in some instances, perhaps the actual saving of life, with adrenocorticotropic and corticosteroid hormone therapy warrants consideration of this disease as the etiologic factor in obscure acute neurologic disorders.

Central nervous system involvement in trichinosis has been described in relatively few cases, but probably occurs more often than the reported cases would indicate. In our small personal experience of about 10 cases of trichinosis at this and a neighboring community hospital in the past few years the 2 cases here reported presented themselves originally with a clinical picture of stupor and delirium suggesting encephalitis of some type.

The clinical and pathologic aspects of central nervous system trichinosis have been reviewed by Hasson and Diamond[4], Most and Abeles[10] and more recently by Hurd[6] and Helfand, Houch and Weissman[5]. The disease has mimicked and been confused variously with (1) meningitis, (2) encephalitis, (3) polyneuritis and radiculitis, (4) cerebrovascular accident, (5) poliomyelitis, (6) acute psychosis and (7) periarteritis nodosa with central nervous system involvement. The symptoms, thus, can vary from evidence of focal lesions as in the case reported by Mavor[8] to meningeal symptoms as reported by Freedman and Clamen[3], encephalitis as in our cases and in the patients described by Roehm[11], Helfand, Houch and Weissman[5] and Hasson and Diamond[4]. In one of the cases discussed by Scott, Johnston and Holzman[15], tetraplegia was the main finding.

The manner in which the lesions are produced easily explains the widespread and diffuse central nervous system involvement. The initial infestation of the body occurs after ingestion of uncooked, or inadequately cooked, pork or bear meat. The adult parasites from the infected meat are released and imbed themselves in the wall of the duodenum or jejunum, where they copulate. During this invasive period, lasting about a week, the symptoms include nausea and vomiting, diarrhea, malaise and fever. At the end of this stage the male worms die, the female worms discharge thousands of larvae, which penetrate the lymphatics and enter the systemic circulation, to be disseminated throughout the body. They lodge in end arterioles, since they are too large to pass through capillaries, and thus are distributed mostly to the myocardium, diaphragm, brain and striated muscle. During this period of about 2 weeks there are marked constitutional

symptoms, with high fever, muscle pains, periorbital edema, and the like. Eosinophilia usually occurs at this time, the eosinophil count averaging perhaps 20 to 35% of the total leukocytes, although much higher percentages may occur.

Microscopic examination of the brain (Hasson and Diamond[4], Most and Abeles[10]) shows varying degrees of inflammatory reaction surrounding the larvae, with thrombosis of arterioles, perivascular edema and cellular infiltration. The infiltration frequently, but not always, contains a goodly proportion of eosinophils. These local changes undoubtedly explain some of the symptoms but do not account for the toxic state which appears in the early phases before the larvae have produced the focal granulomatous lesions. A toxemia has been suggested but thus far no toxin has been demonstrated. Experimental studies by Aikawa, Harrell and Miller[1] have indicated some type of antigen-antibody reaction, with an altered permeability of cellular membranes and a resultant intracellular over-hydration. (An allergic mechanism is the most acceptable explanation both of the reaction and the effect of treatment with corticosteroids—Ed.)

In view of the eosinophilia and the possible antigen-antibody mechanism treatment with ACTH and cortisone naturally suggested itself. Several reports have been published describing the results of treatment in trichinosis in general (Fortier[2], Rosen[12], Sadusk[13], Solomon and Seligman[17], Wertheim and Cohen[18]) and, more recently, in these cases with central nervous system involvement (Meltzer and Bockman[9], Roehm[11]). The symptomatic improvement in these patients has been uniformly striking despite the fact that Luongo, Reed and Weiss[7] showed that, in experimentally infected guinea pigs, there was no evidence of anatomic improvement with use of the hormones.

Brief mention is made here of trichinous myocarditis since one of the patients reported showed definite electrocardiographic evidence of heart muscle involvement. The pathology of this form of parasitic myocarditis has been fully described by Saphir[14]. The larvae are found in the myocardium during the stage of dissemination but apparently do not become encysted as they do in striated muscle. Whether the myocardial dysfunction is due to the edema produced by the reaction to the larvae or again to some antigen-antibody reaction as has been postulated for other manifestations of trichinosis has not been determined. However, full recovery is usually noted if the patient survives, although Roehm[11] describes some persistent abnormalities in his patient demonstrable by ballistocardiography. He described the main features of the electrocardiogram in his patient as low-voltage and T-wave inversions. His patient as well as a case reported by Segar, Kashtan and Miller[16] were treated with ACTH.

Diagnosis. Trichinosis in these cases is usually not suspected at the onset, since eosinophilia and other characteristic findings are often lacking in this phase of the disease. By the same token the patient is often too ill to give an adequate history. Of course the knowledge that the patient has possibly eaten uncooked pork is a prime clue. If the disease is suspected during the stage of invasion adult worms may rarely be found in the diarrheal stool. Muscle biopsy, taken from the deltoid or gastrocnemius, is the mainstay of diagnosis. The typical granulomatous myositis appears early in the disease. Numerous sections may be required, however, definitely to demonstrate the larvae in the area of cellular infiltration. Complement-fixation tests and skin tests may be of value in diagnosis but positive reactions occur in the later stages of the parasitism so that they are

of no help at this stage. Roehm[11] stresses the diagnostic significance of a normal erythrocyte sedimentation rate in a patient who is quite ill and febrile and may or may not have eosinophilia.

Since, as previously noted, the invasion of the central nervous system is widespread, the symptoms and physical findings vary considerably from case to case. There may be various nonspecific complaints such as headache, apathy, drowsiness, stupor, coma and generalized convulsions. Focal findings may include loss of tendon reflexes, hemiplegia, peripheral nerve palsies, peripheral nerve sensory changes, and signs of meningeal irritation including stiff neck.

Case Reports. CASE 1.—Admitted February 24, 1955. Discharged March 25, 1955. A 51-year-old white man, was admitted with the chief complaint of "burning in the chest." Five days before admission he developed mild abdominal cramps and loose, watery stools. Panmycin was given and the diarrhea lessened somewhat but the day after the onset of symptoms he noted severe inflammation of the eyes and conjunctival edema. At the same time he complained of retrosternal "burning" which caused trouble in eating and drinking. Local treatment of the eyes produced some improvement. Since he was not improving rapidly he was admitted to the hospital for further study and treatment.

On physical examination he was found to have moderate edema of the eyelids bilaterally with fairly marked scleral and conjunctival injection. The temperature was 100.2° F., the pulse 90, respirations 18, blood pressure 170/110. The pharynx was diffusely injected and there was moderate edema of the soft palate. No cervical lymphadenopathy was noted. The remainder of the physical examination showed no abnormalities. The urine and blood sugar were normal, a VDRL test was negative, and the blood count was within normal range except for 8% eosinophils. The sedimentation rate was 10 mm. per hour by the Cutler method.

Surprisingly, the morning after admission the patient appeared somewhat somnolent, although he could be aroused to answer questions. However, neurological examination showed no evident abnormalities. As the day went on he became more and more somnolent and by the following day he had lapsed into a deep stupor and could not be aroused to answer questions, nor to take nourishment. Again no localizing neurological signs were elicited and there was no nuchal rigidity. A lumbar puncture showed an initial pressure of 220 mm. of water with normal dynamics. The spinal fluid was clear and colorless, contained 3 leukocytes per c.mm., total protein of 49 mg. per 100 ml. and showed a negative Kolmer test and normal colloidal gold curve.

During the subsequent week he remained stuporous, became incontinent of urine, restless and at times required physical restraint. A second lumbar puncture offered no further information of value, nor did blood chemistry studies, except that a blood count on March 3 again showed an eosinophilia of 8%. A definitive diagnosis had not been made as yet, the possible diagnoses considered being periarteritis nodosa, Hodgkin's disease, or lymphoma, and some type of allergic encephalopathy. During this time he had been receiving a wide gamut of antibiotics, despite which he showed no clinical improvement, the temperature spiking daily to an average of 102° F. rectally, and the pulse ranged from 100 to 120.

On March 4, nine days after admission, a muscle biopsy was taken from the right gastrocnemius muscle and at the same time treatment with 100 mg. of Cortone three times a day was started empirically. The muscle biopsy sections showed large foci of cellular infiltration, the majority of the cells being lymphocytes and macrophages with a small percentage of polymorphonuclear leukocytes and a few eosinophils. One intact parasite of *Trichinella spiralis*, as yet unencysted, was found but the specimen was not serially sectioned to discover other larvae.

Within 24 hours after the Cortone was started the temperature dropped to normal and the pulse rate to 90. The general condition of the patient improved dramatically and by the following day he answered questions intelligently and was able to eat without help. His urinary incontinence persisted for 2 or 3 days and then disappeared. On March 8 he noted some exertional dyspnea and moist rales were heard in the right lower chest. He was digitalized and the rales and dyspnea disappeared. The signs and symptoms of congestive failure had abated and he was allowed out of bed on March 21 and discharged March 25. He has been seen on

numerous occasions since hospitalization, has returned to full activity and has no complaints.

On subsequent investigation after the diagnosis of trichinosis had been established, the fact was elicited that he had eaten some pork sausage purchased at a local butcher shop. It is interesting to note that another patient was under treatment in the hospital at the same time for "sinusitis" and was shown to have trichinosis after it was discovered that she had purchased meat from the same butcher. As far as is known no other cases developed at the time.

The electrocardiographic changes in this patient are of interest, and probably account for the period of congestive failure which developed. No electrocardiograms had been taken prior to hospital admission. On February 26, two days after hospitalization the electrocardiogram showed low to borderline T-waves in all leads. On March 7 the tracing showed inverted T 1,2,3, aVf VI-6. In the light of the diagnosis of trichinosis, which had been made by then, this was interpreted as evidence of trichinous myocarditis, since no digitalis had been given. On March 25, essentially the same T-wave abnormalities existed.

After discharge an electrocardiogram taken on May 27 showed some improvement in that abnormal T-waves had become low upright to flat. The patient still complained of some exertional dyspnea and retrosternal discomfort on climbing stairs. By September 8 he was symptom free and engaged in full work, which required fairly strenuous physical exertion, but the electrocardiographic tracing still showed minor changes as compared to the first one taken in the hospital.

CASE 2.—Admitted January 29, 1958. Discharged March 7, 1958. A white man, age 42, was admitted with the chief complaint of weakness and "sugar." He had been in good health until a few weeks before hospitalization, when he began to note excessive thirst. A week later he complained of a sore throat and numbness in both legs. Two days before admission he developed intractable nausea, with frequent vomiting. There had been some weight loss, some urinary frequency and some shortness of breath on exertion. He was found to have glycosuria and was referred to the hospital for control of the diabetes.

Physical examination after admission showed him to be perspiring moderately, cooperative but definitely confused, and not always understanding the questions asked. The temperature was 103.2° F., the pulse 96 and respirations 24. There were no abnormal findings in the lungs, heart, abdomen or rectum. Neurological examination showed moderate nuchal rigidity, equal but hypoactive deep tendon reflexes at the knee, no cerebellar dysfunction, no sensory changes. The clinical appearance and history definitely indicated diabetes with ketosis but surprisingly, although the blood sugar was 220 mg. per 100 ml., the CO_2-combining power was 26 mEq./L. (58 vol.%) and no plasma or urine acetone was found.

The following day the patient was definitely confused, disoriented and somnolent. The temperature was 104° F., the pulse 100 and respirations 22. The blood pressure was normal. Blood counts showed no abnormalities, the fasting blood sugar was 100 mg. per 100 ml., and a blood culture taken the previous day had shown no growth. A chest roentgenogram showed some increased markings in the left upper lobe with some fine shadows which might have been artefacts. Because of the elevated temperature, the rapid respirations and the vague findings on chest roentgenogram, a diagnosis of pneumonia was considered and antibiotics were administered. He showed no improvement and became progressively more stuporous and confused, the fever persisting. A week after admission a blood count for the first time showed eosinophilia of 13%. The sedimentation rate was 34 mm. per hour (Cutler). In view of the eosinophilia, and our previous experience, the family was questioned carefully and it was learned that the patient frequently would taste the raw sausage his wife purchased, before it was prepared for the table.

A muscle biopsy was taken from the right gastrocnemius muscle and microscopic examination showed large foci of inflammatory cell infiltration, mostly polymorphonuclear leukocytes with a moderate percentage of eosinophils. There was no perivasculitis. On several sections portions of larvae of *Trichinella spiralis* were seen, none of them encysted.

The diagnosis of trichinosis was established on February 11, at which time he was still stuporous, and had fever up to 101° F. Meticorten therapy was started, in a dosage of 20 mg. three times daily. Within 24 hours the temperature had dropped to normal, the stupor and confusion had cleared and within 3 days he was completely normal mentally. He had a slight fever 11 days later, associated with a crop of furuncles in the right groin, which healed in about 2 weeks. He was seen on several occasions after discharge from the hospital and had returned to his usual activities, and offered no complaints.

No further investigation had been made to clarify the glycosuria and hyperglycemia.

Treatment. Administration of the adrenocorticotropic hormones and corticosteroid hormones in the usually recommended doses should be started immediately. One of our cases was treated with Cortone, the other with Meticorten, both with favorable results. Of course general supportive treatment must be utilized as indicated.

Discussion. The symptoms in these cases were sufficiently marked to warrant the diagnosis of "encephalopathy," although, of course, there is no way of knowing what the pathologic changes in the brain were, so that a more specific diagnosis of "encephalitis" cannot be made. Whether or not the manifestations were "toxic" in origin cannot be answered. The dramatic improvement in both cases shortly after administration of steroid hormone therapy must be attributed to treatment rather than to spontaneous remission, although here again there is no absolute proof.

In neither of the cases reported can a definite date be established for the initial ingestion of trichinous meat. In the first case the symptoms suggesting the stage of invasion were quite clear-cut, with abdominal cramps and diarrhea, shortly afterward evidence of localization in the periorbital tissues, and about a week after the onset of symptoms the signs of central nervous system involvement. In the second case the invasive stage is not clearly delineated. The significance of the supposed glycosuria and the elevated blood sugar is not clear and further investigation to establish a diagnosis of diabetes mellitus has not been made.

Summary. Two cases are reported of encephalopathy associated with trichinosis in both of which rapid improvement of symptoms followed steroid therapy. Attention is called to the difficulty of diagnosis in these cases, and it is suggested that the disease be considered in the differential diagnosis of obscure acute neurologic disorders.

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(Interlingua on page 545)

LABORATORY AND CLINICAL DIFFERENTIATION OF CHRONIC GLOMERULONEPHRITIS AND NEPHROSCLEROSIS*

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We have reviewed the laboratory findings, the course, and the necropsy data in patients with histologic evidence of chronic glomerulonephritis or of nephrosclerosis in an attempt to set up clinical criteria for the antemortem differentiation of these entities.

Materials and Methods. On the basis of criteria listed below, 25 instances of glomerulonephritis and 32 examples of arteriolar nephrosclerosis were selected at random from the necropsy files of the Veterans Administration Hospital, Pittsburgh, Pennsylvania. The types and the degrees of histologic alteration were evaluated by the pathologist of the group, E. R. F. Special stains were used when necessary to substantiate impressions gained from examination of sections stained with hematoxylin and eosin. The renal lesions were classified in accordance with the usual criteria (Allen[1,2], Ellis[3]).

1. CHRONIC GLOMERULONEPHRITIS. *A. Diffuse Proliferative (Ellis Type I).* 1. *Acute diffuse proliferative glomerulonephritis.* In cases thus designated, practically all glomeruli appear to be involved in a process characterized by hyperplasia and swelling of endothelial and occasionally epithelial cells of the capillaries. The lumens of the latter are frequently ischemic, although on occasion varying numbers of erythrocytes and neutrophils are present. In addition, focal thrombosis

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†Established Investigator of the American Heart Association.

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and fibrinoid degeneration of the basement membranes are occasionally noted. Although epithelial crescents and synechiæ are found, this change involves only one-third or less of the glomerular lesions in those examples considered as acute. The tubules are frequently spared, although dilatation, casts, and degenerative epithelial changes of moderate degree are occasionally encountered. The interstitium is little affected and the renal vessels appear normal.

2. *Subacute glomerulonephritis.* In this stage epithelial crescents are conspicuous. The crescents are frequently associated with synechiæ formed by the adherence of glomerular tufts to Bowman's capsule. Frequently such formations assume an alveolar or adenomatoid configuration. Proliferative changes within the glomeruli, although evident, are less conspicuous than noted in the acute stage. Thickening and disruption of glomerular basement membranes appear more pronounced in lesions designated as subacute. Obsolete glomeruli are noted, but constitute a minority. Tubular damage appears more severe than in the acute stage, and tends to parallel the degree of glomerular involvement. The stroma is focally thickened and infiltrated with varying numbers of lymphocytes, plasma cells and rarely, neutrophils. Mild to moderate degrees of arteriolar hyalinization are occasionally observed and in some instances the appearance of a rare interlobular artery resembles that encountered in polyarteritis nodosa.

3. *Chronic glomerulonephritis.* More than one-half of the involved glomeruli are obsolete. Crescent formation and, on occasion, proliferative changes similar to those noted in the acute stage are also evident. These latter aid in the differentiation of chronic sclerosing glomerulonephritis from some instances of arteriolar nephrosclerosis. Tubular change is outstanding, being characterized by atrophy, as well as marked epithelial degeneration. Hyaline and granular casts, as well as luminal exudate, are common. The stroma is also severely involved and contains collections of inflammatory cells and fibrosis. The appearance of the renal vessels varies from moderate hyalinization and fibrinoid degeneration accompanied by a mucoid intimal change of the interlobular arteries. Histochemically, this change is characterized by the presence of mucopolysaccharide of the hyaluronic acid type and variable quantities of reticulin and collagen.

It is to be noted however that such a delineation into acute, subacute, and chronic glomerulonephritis is usually arbitrary and largely subjective. One may justifiably inquire exactly how many epithelial crescents are necessary to designate a glomerulonephritis as subacute rather than acute or what percentage of obsolete glomeruli indicate the chronic rather than the subacute stage. This difficulty is further emphasized when it is appreciated that the alterations encountered represent a process rather than a state. It is also obvious that the tempo of the disease is so variable that a clinical estimation of the stage based upon duration of illness may be erroneous.

B. Diffuse Membranous (Allen). This form of glomerulonephritis is characterized by a diffuse thickening of almost all glomerular basement membranes. Such membranes also have an eroded or fragmented appearance readily appreciated in sections routinely stained with hematoxylin and eosin. In addition, the tubules reveal varying degrees of dilatation with casts in their lumens and epithelial degeneration. The renal vasculature appears unaltered.

C. Chronic Lobular (Allen). This type of chronic glomerulonephritis is characterized by a lobular hyalinization of practically all glomeruli. Varying numbers of endothelial cells are also evident in such lesions. Tubular and stromal changes are qualitatively and quantitatively similar to those noted in the membranous form. The differentiation of chronic lobular glomerulonephritis from intercapillary glomerulosclerosis is dependent on the universal glomerular involvement and curleycues of reticulin in the glomeruli demonstrable in appropriately stained sections of the former.

2. NEPHROSCLEROSIS. The evaluation is based on the type and the degree of vascular change.

A. Mild. In examples considered mild, arteriolar hyalinization is relatively focal and luminal narrowing is moderate. Relatively few glomeruli appear altered; these are characterized by a hyaline thickening of the basement membrane which occasionally has a wrinkled appearance, and simplification of capillary tufts. Proliferative glomerular changes and crescent formation are exceedingly rare. Tubular and interstitial alterations are frequently absent, and are only mild when present.

B. Moderate. Lesions considered as moderately severe reveal more diffuse arteriolar changes, as well as more pronounced luminal narrowing. Obsolete glomeruli are by no means infrequent and tubular and interstitial

changes are more severe than those encountered in mild forms of the disease.

C. Marked. Those instances of arteriolar nephrosclerosis considered to be accelerated or marked show fibrinoid degeneration and necrosis of the arterioles and glomerular capillaries, mucoid change of the interlobular arteries and laminated sclerosis of the intima of pre-arterioles.

The more definitive differentiating features of glomerulonephritis and of nephrosclerosis may be summarized as in Table 1:

scribed above permitted ready identification. Further, it was noted that glomerular obsolescence appeared largely to originate within the tuft in the nephrosclerotic kidney, whereas in glomerulonephritis, sclerosis of Bowman's capsule largely contributed to the sclerotic process. The lack of focal cortical aggregates of obsolete glomeruli in chronic glomerulonephritis aided in its differentiation from chronic pyelonephritis.

TABLE 1.—DIFFERENTIAL MORPHOLOGIC FEATURES OF DIFFUSE GLOMERULONEPHRITIS AND ARTERIOLAR NEPHROSCLEROSIS

	Diffuse Glomerulonephritis (25 Cases)	*Arteriolar (32 Cases)*
Predominant lesion	Glomerular	Vascular
General appearance of glomeruli	Large*	Simplified
Number of involved glomeruli	Frequent	Less frequent
Glomerular proliferation; crescents	Conspicuous	Rare
Type of glomerular obsolescence	Frequently originating outside of the tuft	Within tuft
Tubular damage	Severe	Moderate

*In the acute and subacute stages.

Subsequent to this, correlations of the histological findings and the clinical and laboratory data amassed from independent review of the records were made.

Results. 1. RELATIVE FREQUENCY OF HISTOPATHOLOGIC FINDINGS AND THEIR INTENSITY IN THE PITTSBURGH SERIES. Using the above criteria, the differentiation of glomerulonephritis and of arteriolar nephrosclerosis from the histologic point of view offered, for the most part, little difficulty. Occasional instances of chronic glomerulonephritis with severe vascular involvement simulated accelerated arteriolar nephrosclerosis. However, the association of the former with the classical and relatively conspicuous glomerular alterations de-

There were 21 cases considered to be diffuse proliferative glomerulonephritis (Ellis Type I), 2 instances of diffuse membranous nephritis (Allen), and 2 examples of chronic lobular glomerulonephritis (Allen). Pulrely hemorrhagic or exudative glomerulonephritis was not encountered.

Varying degrees of arteriolar nephrosclerosis were found in the 32 examples examined in this study. Twelve were classified as mild, 7 as moderately severe, and 13 as accelerated or severe instances of the disease in accordance with the criteria presented. All examples of accelerated nephrosclerosis in this study revealed some evidence of antecedent chronicity consisting of arteriolar hyalinization, obsolescence of

glomeruli, or atrophic tubular changes.

In 5 patients included in the glomerulonephritis group definite nephrosclerotic changes were also present.

A. Glomeruli. From Fig. 1 it is clear that in our series, taking into account all types and degress of change, the glomeruli were more often spared in nephrosclerosis than in chronic glomerulonephritis, but that slight overlap was present. However, when the number of damaged glomeruli exceeds 75% one can begin to speak of a more definite probability in favor of chronic glomerulonephritis.

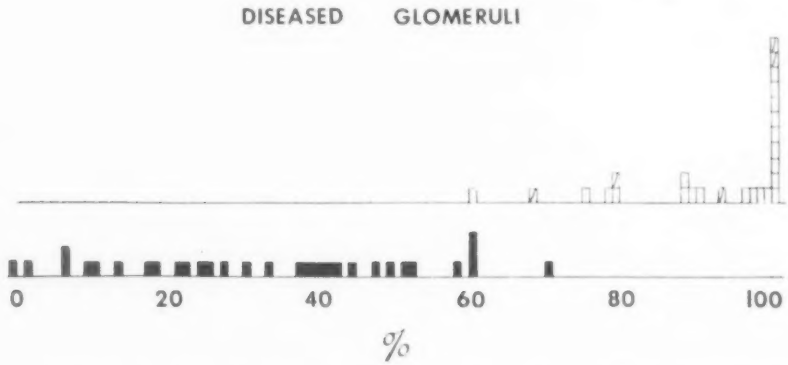


Fig. 1.—Incidence of diseased glomeruli. Open columns refer to chronic glomerulonephritis, solid columns identify nephrosclerosis and a diagonal line through an open column signifies glomerulonephritis with superimposed nephrosclerosis. The percentage of diseased glomeruli, taking into account all types and degrees of change, was generally higher in glomerulonephritis. However, up to 75% involvement may be present in nephrosclerosis.

As might be anticipated, obsolescence, that is, complete destruction of glomeruli, synechiae, polymorphonuclear infiltration, crescent formation, and endothelial proliferation were more common and of greater degree in glomerulonephritis than in nephrosclerosis (Fig. 2). On the horizontal scale the numbers 1, 2, and 3 refer to mild, moderate, and marked changes, respectively. Goormaghtigh bodies or calcification were quite infrequent in both diseases and have not been included in the diagram.

Insofar as the basement membranes in these examples of the two entities were concerned, it is evident from Fig. 2 that focal thickening and the wire type, the fibrinoid and the hyaline changes were either of minor degree in nephrosclerosis or absent. Diffuse thickening of moderate intensity; that is, 2+, was noted in the majority of the nephrosclerotic patients. Marked changes, namely 3+, were observed only in glomerulonephritic or mixed glomerulonephritic-nephrosclerotic specimens.

B. Tubules. The bulk of the nephrosclerosis cases in this series showed mild or moderate tubular disease, if any, as evidenced by the presence of dilatation, hyalinization of the basement membrane, degeneration or necrosis and regeneration and the presence of exudate and casts. By contrast the kidneys of patients with chronic glomerulonephritis were usually found to contain these changes to a moderate

or marked degree (Fig. 3). These data indicate also that tubular involvement in nephrosclerosis and in glomerulonephritis is of the same type but differs in intensity.

2. CLINICAL COURSE AND CORRELATION OF CLINICAL AND LABORATORY FINDINGS. At the onset it must be emphasized that this is a biased picture of the natural history of chronic glomerulonephritis

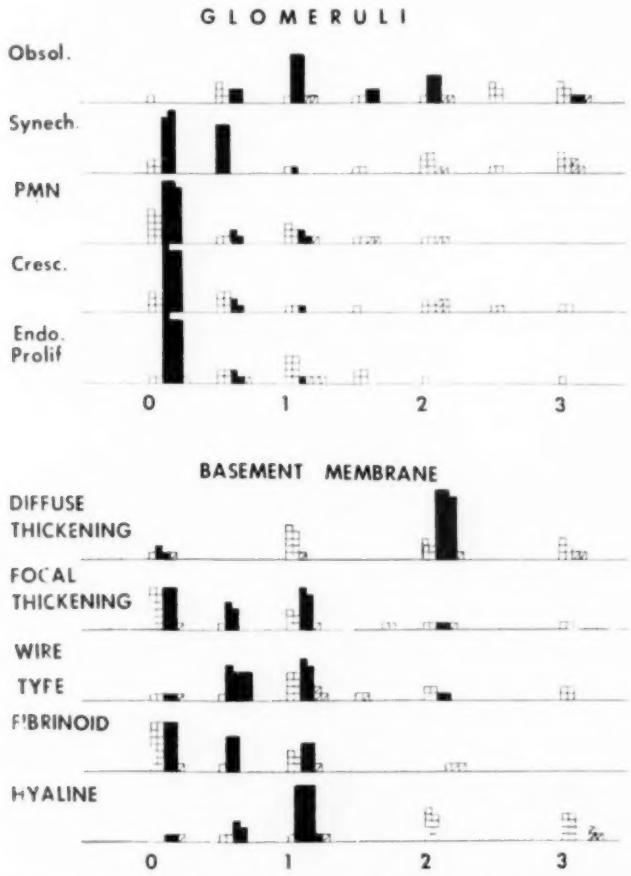


Fig. 2.—Frequency of glomerular and basement membrane changes in nephrosclerosis (solid squares), chronic glomerulonephritis (open squares), and in chronic glomerulonephritis with nephrosclerosis (open squares with diagonal). 0, 1, 2, and 3 refer to none, mild, moderate, and marked changes, respectively.

C. Stroma. Similarly, the stroma or interstitium of patients with glomerulonephritis in general showed a greater degree of scar tissue formation and of infiltration by lymphocytes, polymorphonuclear leukocytes and plasma cells (Fig. 3).

and of nephrosclerosis. These are all patients who have died and hence both groups are undoubtedly weighted by an undue proportion of the more severe forms and hence the more rapidly fatal instances of the disease. The patients with glomerulonephritis were

somewhat younger, 31 years versus 34 years, at the onset of the illness, but glomerulonephritis at the age of 50 or later was recorded three times. Those with glomerulonephritis on the average survived 3 years and 2 months compared to 3 years and 5 months in the nephrosclerotic group.

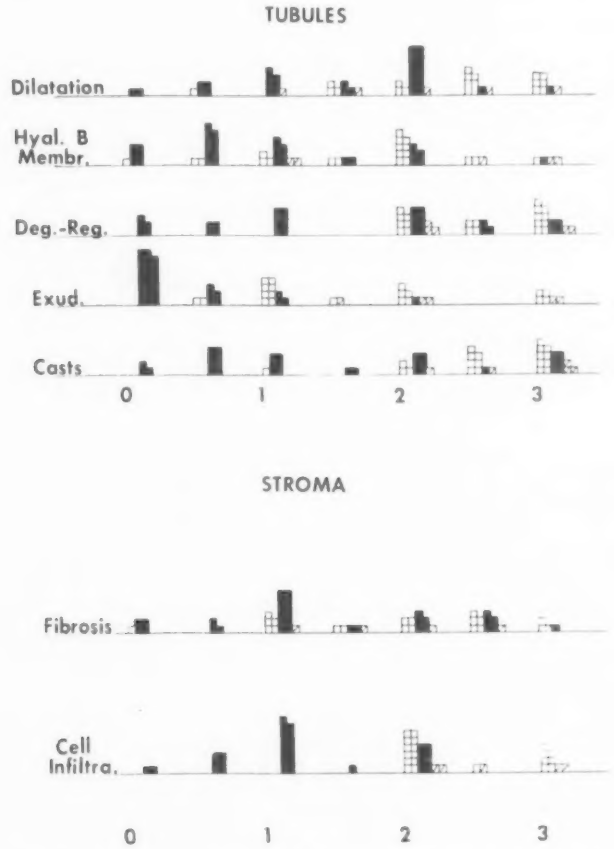
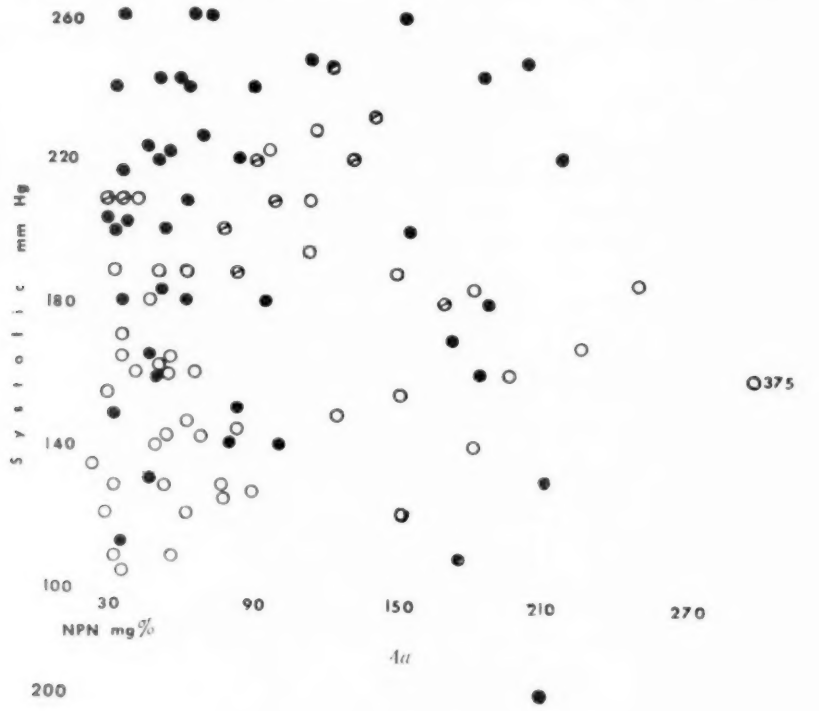


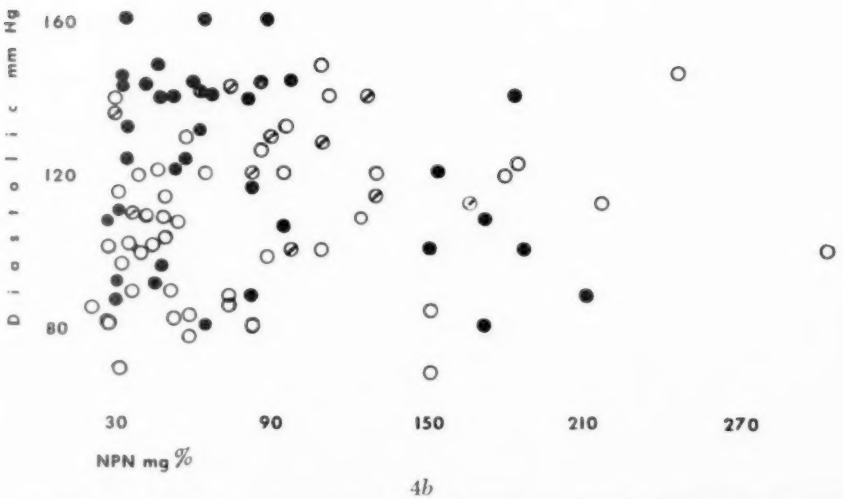
Fig. 3.—Tubular and stromal alterations. Symbols as in Fig. 2.

A. The Histologic Lesions Related to the Level of Blood Pressure and NPN. From Figs. 4*a* and 4*b* it is evident that in patients with nephrosclerosis the blood pressure, both systolic and diastolic, tended to be higher than in entities classified as glomerulonephritis. The findings in Figs. 4*a* and 4*b* also illustrate that patients with nephrosclerosis were much more apt to have systolic hypertension at a time when the whole blood nonprotein nitrogen values were within the normal range, or only slightly elevated. The patients with glomerulonephritis tended to manifest however a rising systolic pressure as renal failure progressed. This did not appear to be the case in nephrosclerosis, though observations in the latter stages of uremia were rare in this group.

Though not illustrated in a figure,



4a



4b

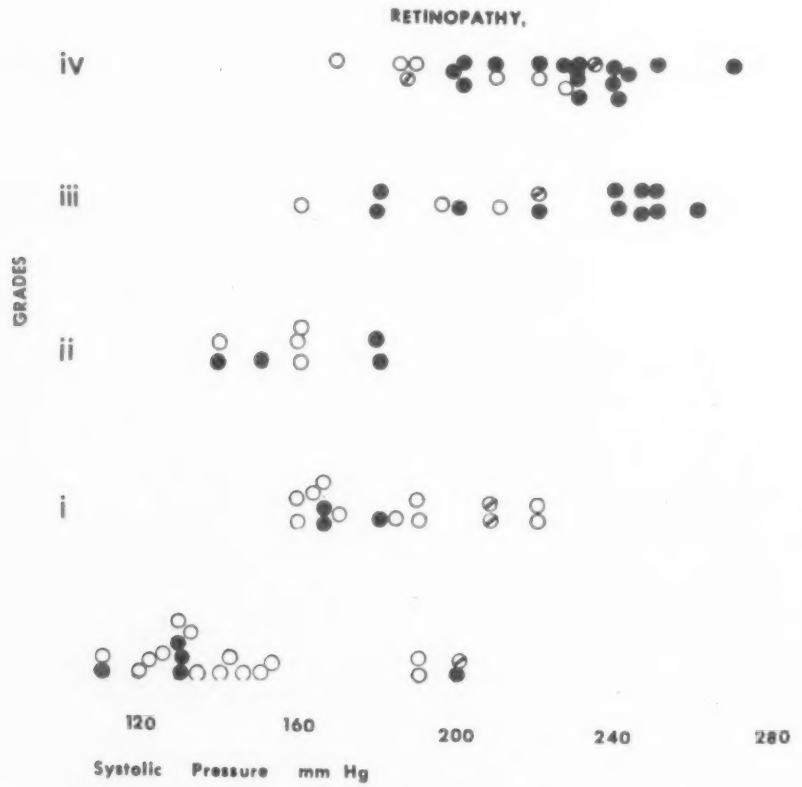
Figs. 4*a* and *b*.—Tendency to greater degrees of systolic and diastolic hypertension occurring earlier in relation to azotemia in nephrosclerosis (solid circles) compared to chronic glomerulonephritis (open circles). Open circles with bar identify patients with nephritis and nephrosclerosis. Data are based on minimal systolic and diastolic blood pressure readings in relationship to one or more determinations of the whole blood nonprotein nitrogen.

TABLE 2.—INCIDENCE OF CHANGES IN ARTERIOLES IN RELATION TO SYSTOLIC AND DIASTOLIC BLOOD PRESSURES*

		Systolic (Bl.P. <180)		*Systolic (Bl.P. 180+)*		*Diastolic (Bl.P. <100)*		*Diastolic (Bl.P. 100+)*	
		N.Scl.	*Gl.N.*	*N.Scl.*	*Gl.N.*	*N.Scl.*	*Gl.N.*	*N.Scl.*	*Gl.N.*
	None	100†	75	53	33	66	83	50	33
Fibrinoid Change	Mild	0	25	27	66	0	17	21	66
	Moderate	0	0	7	0	33	0	0	0
	Marked	0	0	14	0	0	0	29	0
	None	0	30	3	30	10	44	6	29
Hyalinization	Mild	38	50	39	40	20	50	35	35
	Moderate	44	20	24	30	50	6	29	35
	Marked	19	0	33	0	20	0	29	0

*The five cases of glomerulonephritis with nephrosclerosis have been excluded from the calculations.

†% of the 32 cases of nephrosclerosis and the remaining cases of glomerulonephritis.

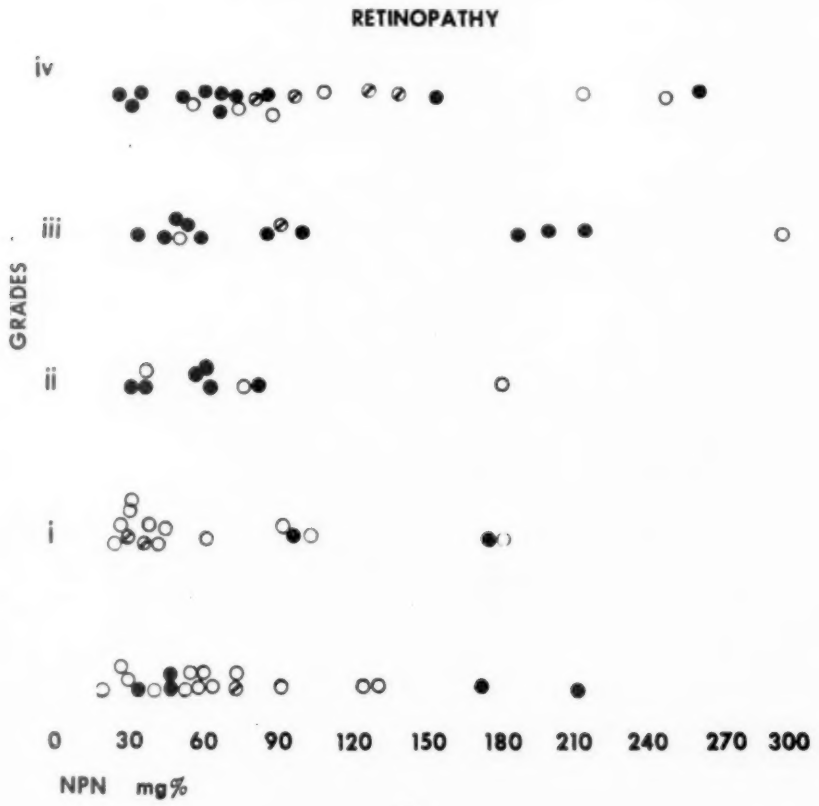


5*a*

the higher systolic and diastolic blood pressure readings were in general associated with the more severe histologic changes in nephrosclerosis. This was not an absolute relationship, however, since occasional mild or moderate histopathologic alterations were observed in patients with marked hypertension while in others severe nephrosclerosis was not associated with pronounced elevation of the blood pressure. Moreover, the hyalinization but not the fibrinoid changes in the arterioles proved to be more pronounced in patients with the higher degrees of systolic and diastolic hypertension (Table 2).

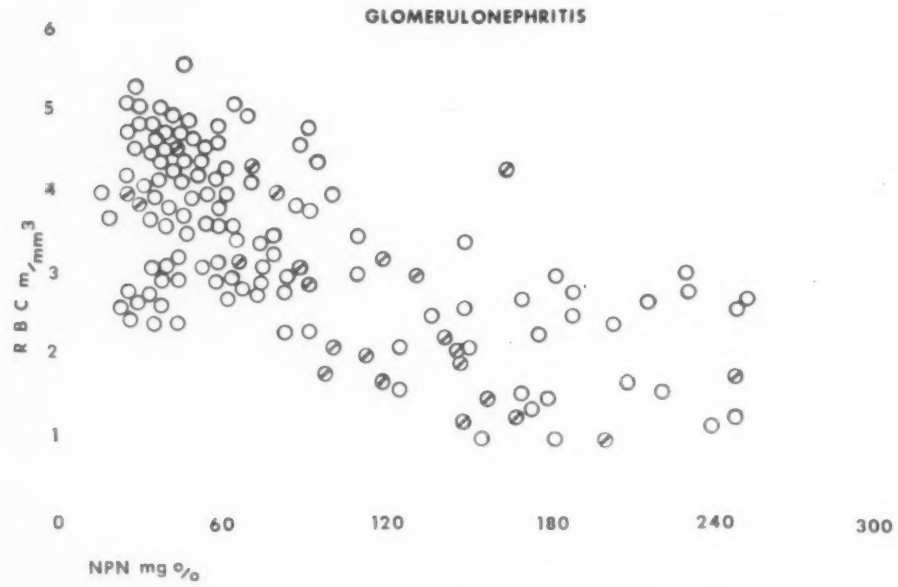
B. Graded Retinopathy in Relation to Systolic and Diastolic Blood Pressure and to Nonprotein Nitrogen Levels. In Fig. 5*a* a trend to increasing degrees of retinopathy in patients with progressive elevations of systolic and in diastolic blood pressure is apparent. This tendency was more pronounced in those with nephrosclerosis.

It is to be noted that in general patients with nephrosclerosis tended to have more marked degrees of retinopathy at a time when mild degrees of azotemia were present (Fig. 5*b*).

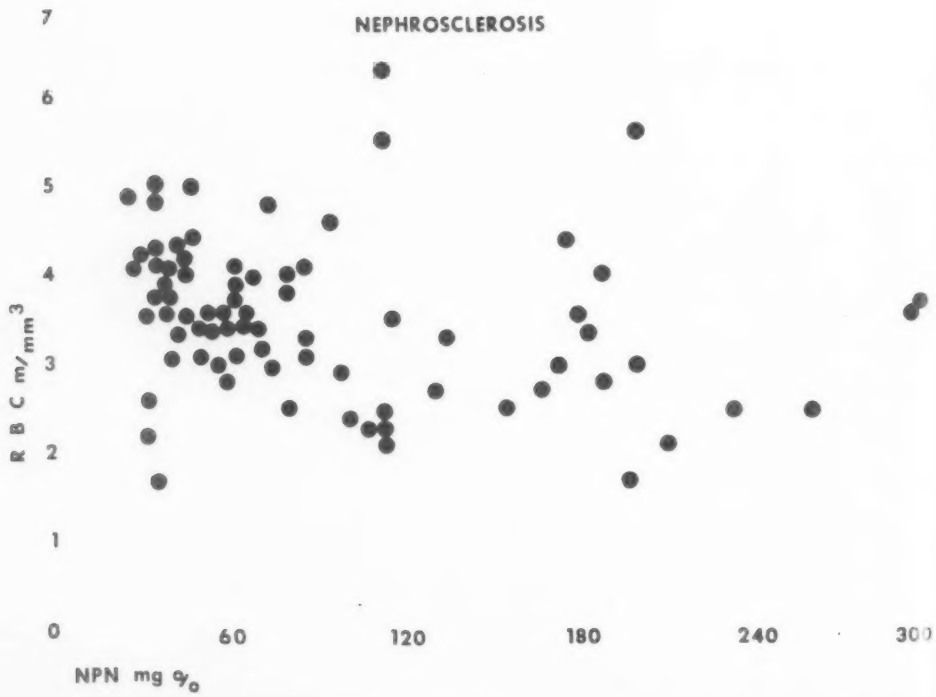


5*b*

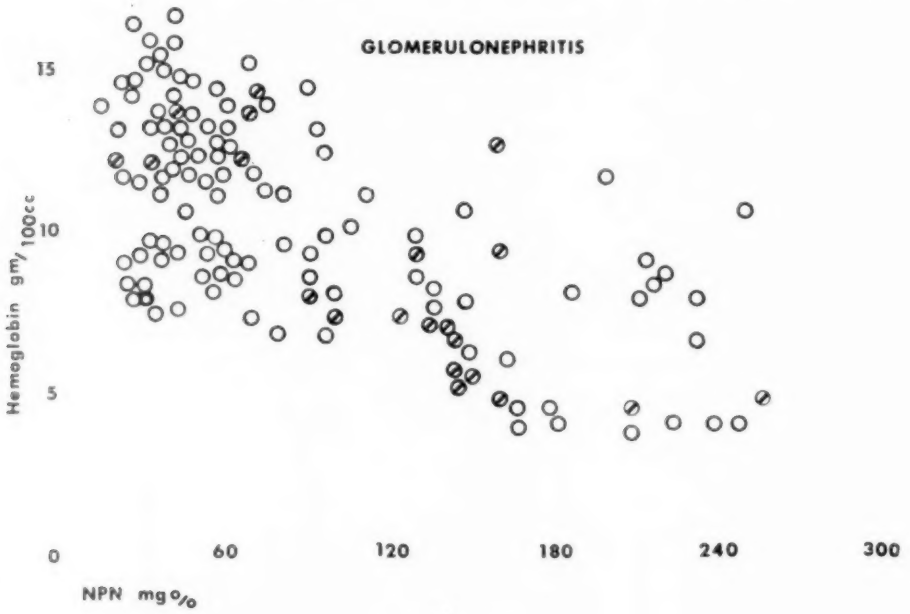
Figs. 5*a* and *b*.—The greater degree of retinopathy in nephrosclerosis correlating with the hypertension. Observations at more than one level of hypertension were available in most patients.


GLOMERULONEPHRITIS
R B C m/mm3
6
5
4
3
2
1
0
60
120
180
240
300
NPN mg %

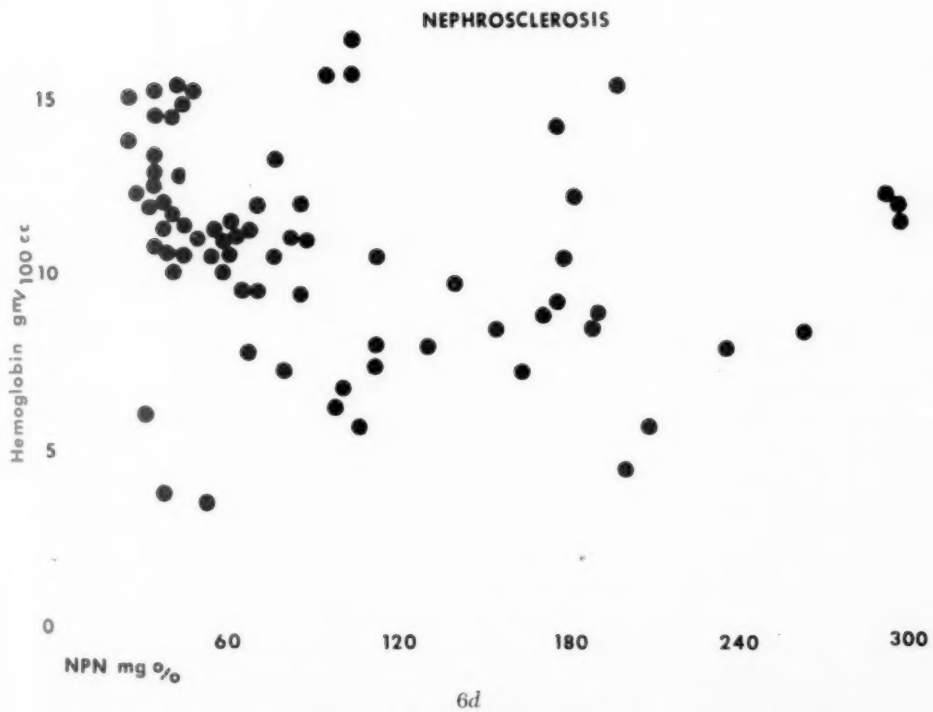
6a


NEPHROSCLEROSIS
R B C m/mm3
7
6
5
4
3
2
1
0
60
120
180
240
300
NPN mg %

6b



6c



6d

Figs. 6*a* through *d*.—Earlier onset and more profound degrees of anemia in relationship to azotemia in chronic glomerulonephritis than in nephrosclerosis.

C. *Anemia and Leukocytosis in Relationship to Azotemia in Chronic Glomerulonephritis and in Nephrosclerosis.* The two groups of patients are distinguishable early in azotemia with regard to the onset, frequency, and degree of erythrocyte and hemoglobin decrease. Figures 6*a* through 6*d* show that in patients with nephrosclerosis not previously transfused, anemia in the early phase of azotemia occurred less often than in patients with glomerulonephritis. However, when nonprotein nitrogen values of 90 to 120 were recorded, virtually all patients showed a lowering of the erythrocyte count and of the hemoglobin concentration, though again this was less marked in nephrosclerosis. This simple correlation does not establish, of course, that the anemia was directly related to the azotemia *per se* and not to malnutrition or similar nonrenal factors.

Though not presented graphically, leukocyte counts below 5000 per c.mm. were extremely rare at any time in patients with nephrosclerosis or glomerulonephritis, whereas leukocytosis above 10,000 per c.mm. was present with equal frequency in both groups in about 50% of the patients. It was noted that this was an accompaniment of the earlier phase of the illness, that is, when the nonprotein nitrogen levels were only slightly elevated, if at all. The dearth of values in patients in advanced azotemia does not permit as definite a statement, but a comparable trend appears to have been present.

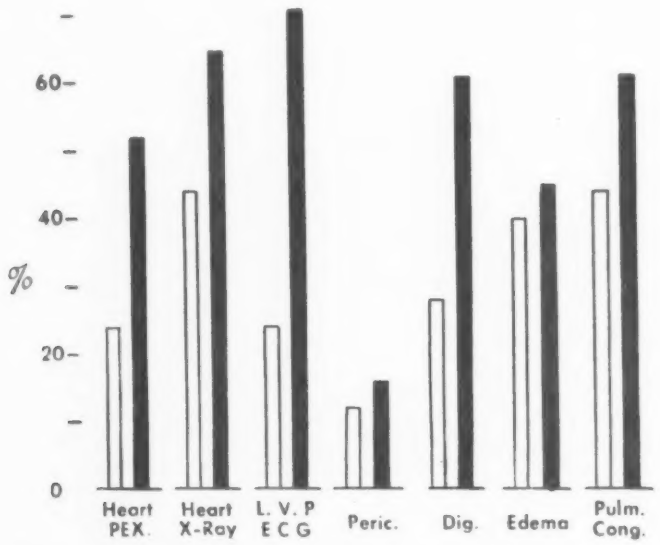
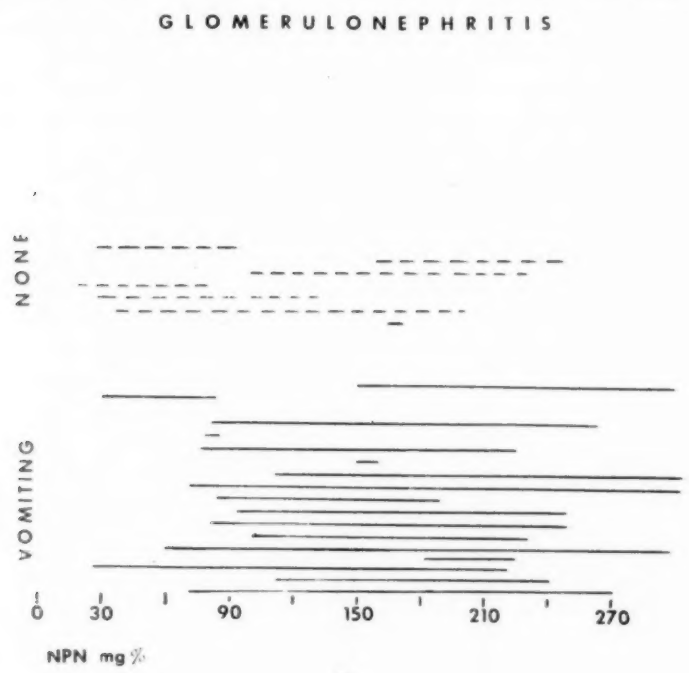
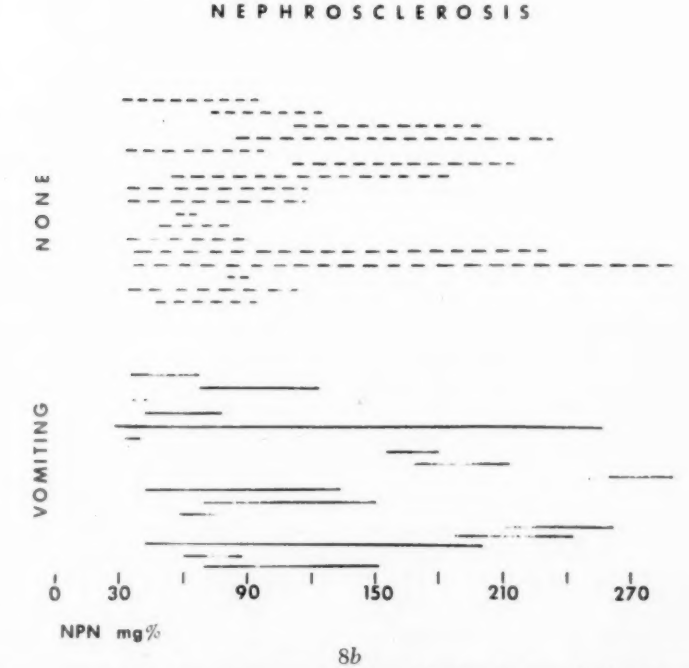


Fig. 7.—Greater incidence of most cardiovascular complications in nephrosclerosis.

D. Cardiovascular Changes. From Figure 7 it is evident that patients with nephrosclerosis who in general had greater degrees and a higher incidence of systolic and diastolic hypertension also had cardiomegaly more often as indicated by physical examination, teleoroentgenography, and the presence of left ventricular preponderance in the electrocardiogram. Also, such patients developed pulmonary congestion and were digitalized more often. The incidence of pericarditis and of



8*a*



8*b*

Fig. 8.—Occurrence of vomiting. Horizontal solid and broken lines each identify an individual. Patients with nephrosclerosis vomited earlier than those with glomerulonephritis and at a time when nonprotein nitrogen values were normal. However, as the azotemia increased the nephritics vomited more often and for more protracted periods.

edema, however, was the same in the two groups.

E. The Occurrence of Vomiting in Relation to Azotemia and to Hypertension. Patients with nephrosclerosis as a group tended to vomit at lower levels of nonprotein nitrogen than those with glomerulonephritis. Though not shown in the figure, this tendency correlated highly with the presence of systolic hypertension. However, at nonprotein levels of 90 mg. per 100 ml. vomiting occurred more often and was more protracted in the chronic nephritic group. Occasional patients in both groups continued without this complaint up to the time of their demise (Figs. 8*a* and 8*b*).

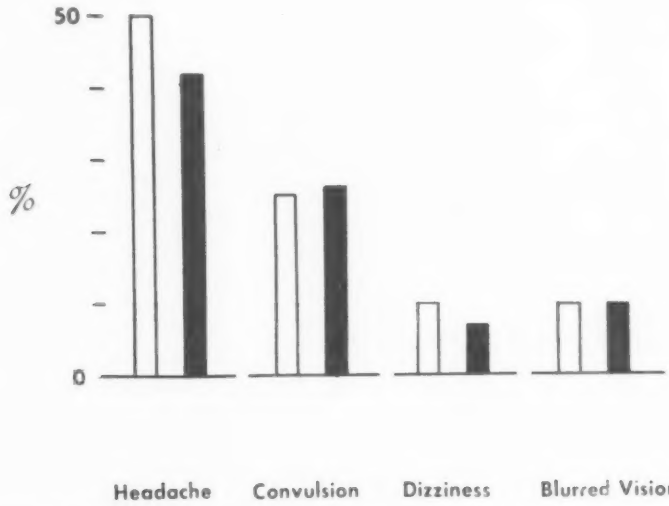


Fig. 9.—Approximately equal frequency of encephalopathy in nephrosclerosis and chronic glomerulonephritis. See text for comment on vomiting.

F. Encephalopathic Manifestations. There was no significant difference in the frequency of headaches, convulsions, dizziness, or blurring of vision among members of the two groups. The actual incidence is shown in Fig. 9.

Discussion. The clinical identification of chronic glomerulonephritis or of nephrosclerosis has always presented a problem. In any patient with hypertension and renal disease, entities such as Goldblatt kidney, pyelonephritis, amyloidosis, hyperparathyroidism, gout, intercapillary glomerulosclerosis or myelomatosis can usually be identified by one of several relatively simple laboratory procedures. However in the case of chronic glomerulonephritis and of nephrosclerosis such distinguishing laboratory findings are lacking and the urinary findings are usually not distinctive. Since these two diseases are the commonest form of nephropathy extant, the studies herein described provide a basis for an order of probability for their clinical differentiation. Though percutaneous needle biopsy of the kidney would often provide a diagnosis without recourse to such exercise of clinical judgment, the technique is not universally available nor without hazard. Thus certain aphorisms

appear justifiable, provided it be kept in mind that, as with clinical experience in general, it is always easier to discuss probabilities in diagnosis and outcome in groups of patients rather than in specific individuals.

Assuming that other renal entities have been excluded or appear unlikely and that the patient has either glomerulonephritis or nephrosclerosis, then: the lower the blood pressure in a patient with proteinuria the more likely the possibility of chronic glomerulonephritis; though glomerulonephritis is a disease of the earlier decades and mild nephrosclerosis is more apt to occur in the later life span, our series illustrates that there may be little, if any, difference in the ages at the time of involvement or death of patients with fatal forms of these diseases; extensive retinopathy argues for nephrosclerosis; hypertension before azotemia favors nephrosclerosis; the greater the anemia, the more likely the possibility of glomerulonephritis; vomiting in a nonazotemic hypertensive suggests nephrosclerosis; finally, cardiovascular manifestations but not encephalopathy are more frequent in nephrosclerosis.

Summary. 1. The frequency, the extent and the intensity of change in the nephron, the vessels and the stroma of the kidneys of 32 males with nephrosclerosis and 25 others with glomerulonephritis have been related to the clinical manifestations.

2. There was no evident difference in the age of onset, the duration of proteinuria, the length of survival, the time of onset and duration of azotemia, or the length of survival in these two groups.

3. As a group, patients with nephrosclerosis were found to have hypertension earlier and to a greater degree in relation to azotemia, and as a matter of fact, often antedating this manifestation of renal disease.

4. Patients with chronic nephritis tended to develop progressive hypertension as the degree of azotemia increased, but the systolic and diastolic rise was usually of a lesser order of magnitude compared to the nephrosclerotics.

5. A trend to increasing degrees of retinopathy with rising systolic and diastolic pressure readings was recorded in both groups. This was more pronounced in patients with nephrosclerosis, in whom marked retinopathy was often also present when azotemia was mild.

6. Anemia appeared early in the course of azotemia in about one-half of the members in each group but was not as marked in nephrosclerosis as in glomerulonephritis. At a whole-blood nonprotein level of 120 mg. per 100 ml. or higher, virtually all patients in both groups manifested a decrease in erythrocytes and in hemoglobin, but ultimately anemia appeared to be greater in the glomerulonephritics.

7. Leukocytosis was recorded in 1 out of 2 patients in each category; leukocyte counts of 5000 per c.mm. or less were quite infrequent.

8. Patients with nephrosclerosis tended to vomit earlier than those with glomerulonephritis, and this occurred even when the nonprotein nitrogen levels were virtually normal. However, with moderate elevations of the nonprotein nitrogen, those with glomerulonephritis vomited more often and for more protracted periods.

9. Cardiovascular complications occurred more often in nephrosclerosis. This was not true of encephalopathy, unless early vomiting in nonazotemic nephrosclerosis is thus interpreted.

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3. **Ellis, A.:** Lancet, **1**, 1, 1942.

SUMMARIO IN INTERLINGUA

Differentiation Laboratorial E Clinic Inter Chronic Glomerulonephritis E Nephrosclerosis

1. Le frequentia, le extension, e le intensitate del alteration del nephron, del vasos e del stroma del renes de 32 masculos con nephrosclerosis e de 25 alteres con glomerulonephritis esseva ponite in relation con le manifestationes clinic.

2. Esseva constatate inter le duo gruppos nulle differentia in le etate del patientes al tempore del declaration del morbo, in le duration del proteinuria, in le periodo de superviventia, o in le tempore del declaration e le duration de azotemia.

3. Esseva trovate que le patientes con nephrosclerosis, reguardate como un gruppo, habeva hypertension a plus alte grados e a un tempore plus precoce in relation al declaration de azotemia. De facto le hypertension occurreva frequentemente ante que le morbo renal habeva resultate in azotemia.

4. Patientes con nephritis chronic tendeva a disveloppar hypertension progressive durante que le grado del azotemia montava, sed le augmento systolic e diastolic del hypertension esseva usualmente de un ordine inferior a illo notate in patientes con nephrosclerosis.

5. Un tendentia a disveloppar retinopathia de grados montante durante que le lecturas del pression systolic e diastolic ascendeva esseva notate in ambe gruppos. Iste phenomeno esseva plus marcate in le patientes con nephrosclerosis. In illes, marcate grados de retinopathia esseva frequentemente presente quando le azotemia esseva ancora leve.

6. Anemia appareva precocemente in le curso del crescentia de azotemia in circa un medietate del subjectos in ambe le gruppos, sed iste anemia esseva minus marcate in casos de nephrosclerosis que in casos de glomerulonephritis. A nivellos de nitrogeno non-proteinic amontante a 120 mg (o plus) per 100 ml de sanguine integre, quasi omne le patientes in ambe gruppos manifestava un reduction del numeration erythrocytic e del concentration hemoglobinic, sed ultimemente le anemia pareva esser plus pronunciate in le patientes con glomerulonephritis.

7. Leucocytosis esseva constatate in un medietate del patientes in ambe gruppos. Numerationes leucocytic de 5000 per mm^3 o minus esseva satis infrequente.

8. Patientes con nephrosclerosis tendeva a vomer plus precocemente que patientes con glomerulonephritis, e isto occurreva mesmo quando le nivellos de nitrogeno non-proteinic esseva practicamente normal. Tamen, in le presentia de moderate augmentos del nivellos de nitrogeno non-proteinic, subjectos con glomerulonephritis vomiva plus frequentemente e plus prolongatemente que le subjectos con nephrosclerosis.

9. Complicationes cardiovascular occurreva plus frequentemente in nephrosclerosis. Isto non esseva ver pro encephalopathia, excepte si on vole interpretar le occurrentia precoce de vomito in casos de nephrosclerosis non-azotemic in iste senso.

POSTDIALYSIS ACID-BASE BALANCE OF PATIENTS WITH CHRONIC UREMIA*

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Chronically ill patients having the uremic syndrome show variable responses to the procedure of external hemodialysis. Clinical improvement may not be apparent for a few days following dialysis and then may occur in spite of the return of the concentration of nitrogenous metabolites in the blood toward predialysis levels (Merrill[6]). The reasons for both the variability and the delay in clinical improvement are not known. The alterations during hemodialysis in the acid-base balance of patients having chronic renal insufficiency have been reported previously (Weller, Swan and Merrill[15]). The purpose of this study is to describe the changes in the acid-base balance in the postdialysis period and to correlate these chemical changes with the clinical course of these patients.

Methods. Five patients with chronic renal insufficiency were studied. Hemodialysis was applied for 5 or 6 hours to each by means of a modified Kolff-type artificial kidney (Murphy *et al.*[7]). Arterial or arterialized venous blood was collected anaerobically and analyzed for serum pH by the method of Hastings and Sendroy[5]; total CO_2 content, Van Slyke and Neill[14]; blood urea nitrogen, Archibald[1]; serum sodium and potassium with a Barclay flame photometer using lithium as an internal standard; serum chloride, Schales and Schales[9]; serum phosphorus, Fiske and Subbarow[3]; and serum calcium, Clark and Collip[2].

The values of the components describing the acid-base balance of the blood have been derived from the nomogram of Singer and Hastings[11]. The metabolic component, or whole blood buffer base, $(B_{B^-})_b$, is the concentration of cation equal to the sum of the buffer anions. The principal buffer anions are bicarbonate and protein (including hemoglobin). A diminished total buffer anion concentration by definition is a metabolic acidosis. The buffer base is also equal to the difference between the sum of the cations (total base)‡ and the total nonbuffer anion concentration. Alterations in these constituents in chronic renal insufficiency consist of either a total base deficit (hyponatremia) or

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‡The term "base" is here used to conform to the precedent of Singer and Hastings although the Bronsted definition is more accurate (Relman[8]).

a "fixed acid" (nonbuffer anion) excess. The primary change in the acid-base balance of these patients is a metabolic acidosis with a decreased buffer base.

The respiratory component of the acid-base balance is the partial pressure of carbon dioxide (P_{CO_2}) of arterial blood (or alveolar air). This respiratory component may undergo rapid primary deviations with alterations in the respiratory exchange of carbon dioxide. A diminished P_{CO_2} by definition is a respiratory alkalosis while an increased P_{CO_2} is a respiratory acidosis. "Compensatory" or secondary changes in the P_{CO_2} may also occur and tend to minimize the deviation of the serum pH from normal. In chronic renal insufficiency the primary metabolic acidosis may be accompanied by a secondary respiratory alkalosis (low P_{CO_2}).

Clinical Material and Results. CASE 1. H.O., a 21-year-old man had polycystic kidney disease. He had weakness, malaise, and muscle cramps for 8 weeks prior to admission. During the 2 weeks before admission he had persistent vomiting which necessitated hospitalization for intravenous fluid therapy. Because of failure to improve he was transferred to this hospital. Physical examination

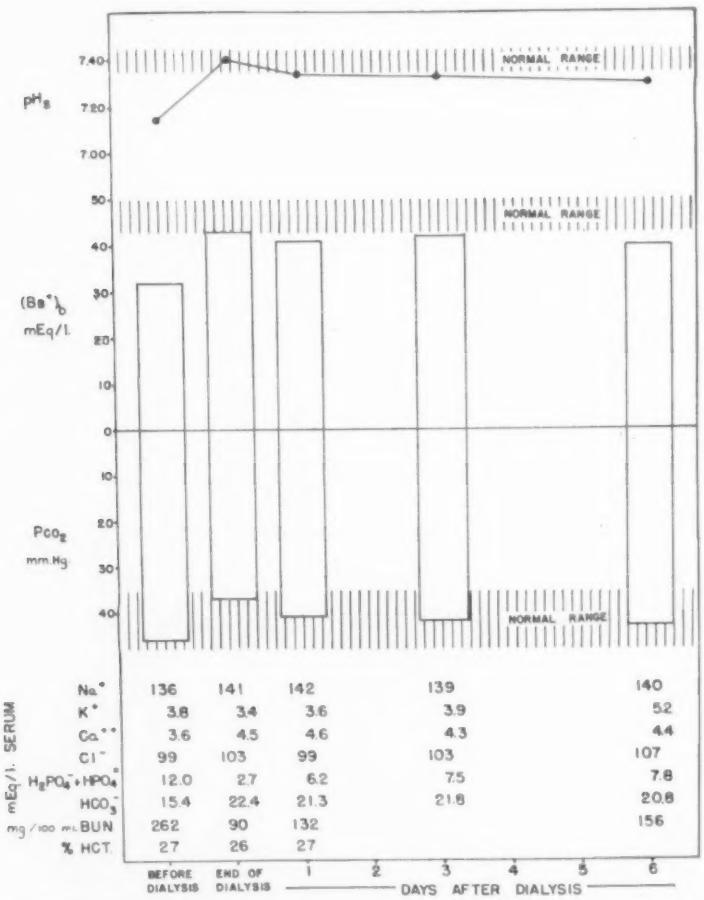

Fig. 1.—Determined and derived values of the serum pH, pHs, the whole blood buffer base, $(B_B^-)_b$, the partial pressure of carbon dioxide, P_{CO_2}, and the serum electrolytes, blood urea nitrogen, BUN, and hematocrit, HCT, of patient H.O.

showed the blood pressure to be 130/80 mm. Hg. The heart and optic fundi were normal. Both upper abdominal quadrants were full on palpation. Reflexes were hyperactive. Urine examination showed a specific gravity of 1.013, 1+ protein, and the centrifuged sediment contained 2 to 3 red blood cells and 20 to 25 white cells per high power field. The total serum protein was 6.6 gm. per 100 ml. Twenty-four hour urine volumes averaged 900 ml. Further intravenous fluids did not result in any improvement in his clinical state and on the ninth hospital day hemodialysis was performed.

The components describing the acid-base balance of the blood and the concentrations of the serum electrolytes before and after hemodialysis are shown in Fig. 1. The metabolic acidosis (decreased buffer base) was alleviated by dialysis. The serum pH returned to normal. These components showed only slight tendency to return to their previous levels during the immediate postdialysis period. Two days after hemodialysis was performed the patient ceased vomiting and noted an increase in his muscular strength. The next day he was able to eat a 2000 calorie diet. He was discharged on the sixth day after hemodialysis and died 37 months later.

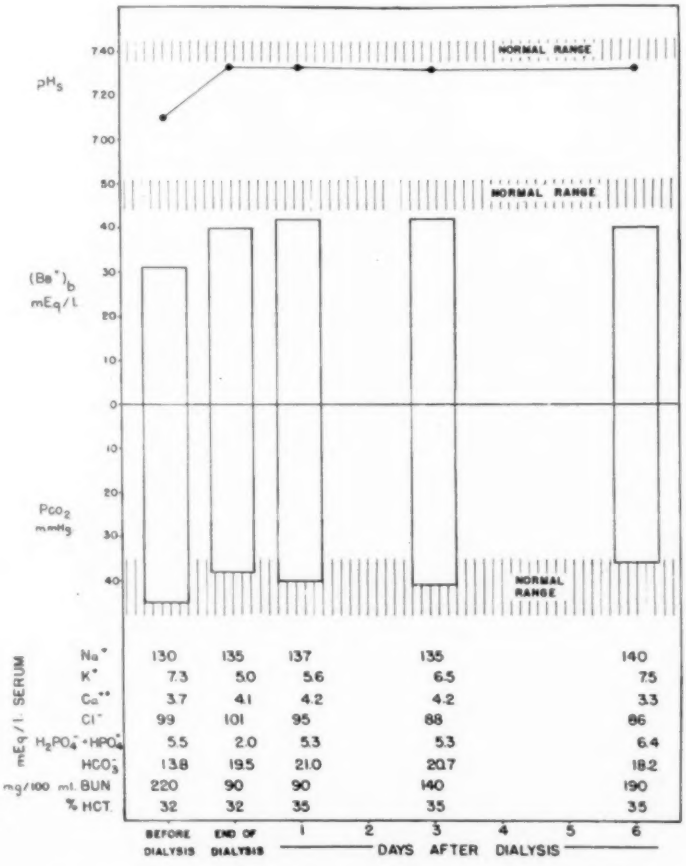

Fig. 2.—The determined and derived values of patient E.M.

CASE 2. E.M., a 42-year-old man, had known polycystic kidney disease. For one year, fatigue, muscular cramps and weight loss had been present. He was referred to

this hospital because of increasing nausea and vomiting. Physical examination disclosed a blood pressure of 170/110 mm. Hg. The heart was normal. Each upper abdominal quadrant was filled with a lobulated mass. Muscular fasciculations were present. The serum protein was 6.5 gm. per 100 ml. Urine examination showed a specific gravity of 1.008, 1+ protein, and the centrifuged sediment contained 25 to 40 red blood cells and 10 to 15 white blood cells per high power field. The changes in the acid-base balance and serum electrolytes following hemodialysis are shown in Fig. 2. On the second postdialysis day, nausea and vomiting ceased and the patient noted a marked diminution in the severity of his muscular cramps. He was discharged from the hospital 6 days after dialysis.

CASE 3. G.T., a 41-year-old man, was known to have hypertension since the age of 14. Diagnoses of pyelonephritis and hypoplastic left kidney had been made. Three years prior to admission, a nephrolithotomy was performed on the right kidney. Symptoms of uremia had become progressively more severe. For the 2 weeks prior to admission he had persistent nausea and vomiting. He was hospitalized because of marked shortness of breath and headache. Physical examination showed a blood pressure of 230/140 mm. Hg, numerous exudates and hemorrhages

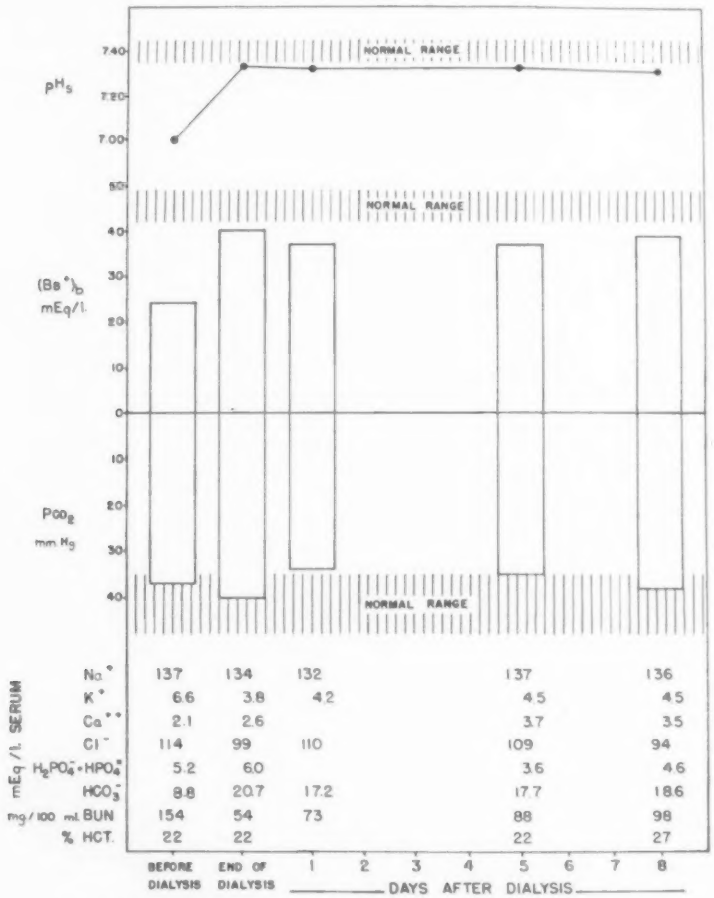

Fig. 3.—The determined and derived values of patient G.T.

in both optic fundi, cardiomegaly, and hepatomegaly. The serum protein was 5.0 gm. per 100 ml. Urine examination disclosed 3+ protein and numerous red cells, white cells and granular casts in the sediment. The 24-hour urine output averaged one liter. The patient showed no clinical improvement on

tained during the ensuing 8-day period. On the first postdialysis day the patient was able to walk and on the second day his appetite improved so that he was then able to be maintained on oral fluids. He was discharged on the eighth day after dialysis and returned home to limited physical activity.

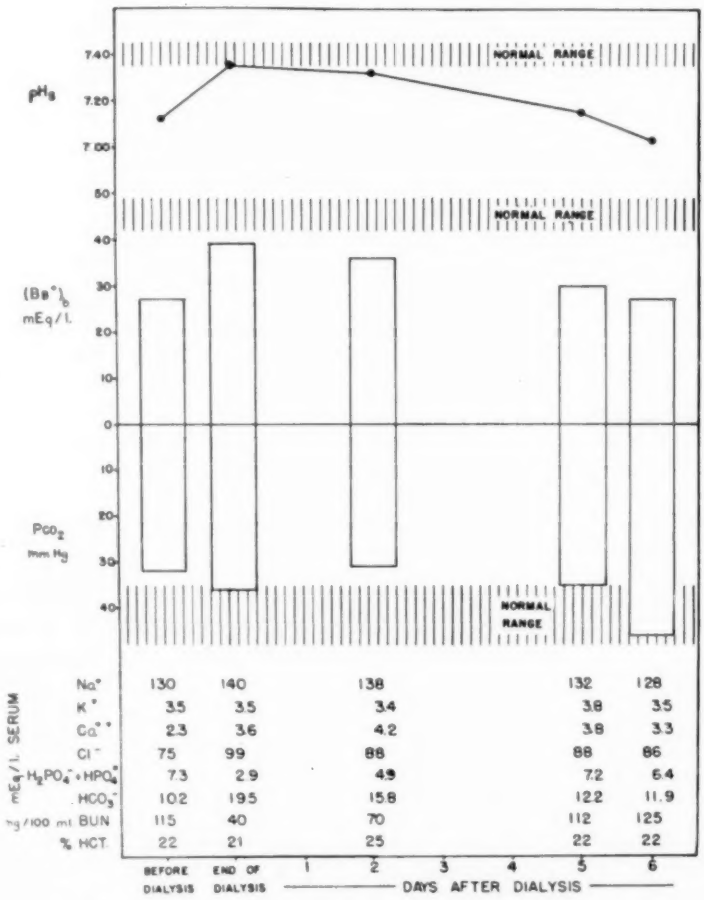

Fig. 4.—The determined and derived values of patient H.H.

conservative therapy and, therefore, hemodialysis was performed. Figure 3 shows the changes effected in the acid-base balance and serum electrolyte composition. This patient had a more severe metabolic acidosis prior to dialysis than did the previous two, but the degree of nitrogen retention was not as marked. The chemical changes resulting from dialysis were again quite well main-

CASE 4. H.H., a 37-year-old man, had acute glomerulonephritis at the age of 17 and subsequently had several exacerbations. He developed acute pulmonary edema 10 months prior to admission and hypertension and azotemia were noted. Since that time he had increasing nausea and vomiting which became so severe that hospitalization was necessary. In spite of intravenous fluid therapy

his condition deteriorated and convulsions ensued. On transfer to this hospital physical examination disclosed a blood pressure of 180/100 mm. Hg, exudates in the optic fundi, and cardiomegaly. Urine examination showed 1+ protein and rare white cells, red cells, waxy and granular casts in the sediment. The serum protein was 5.9 gm. per 100 ml.

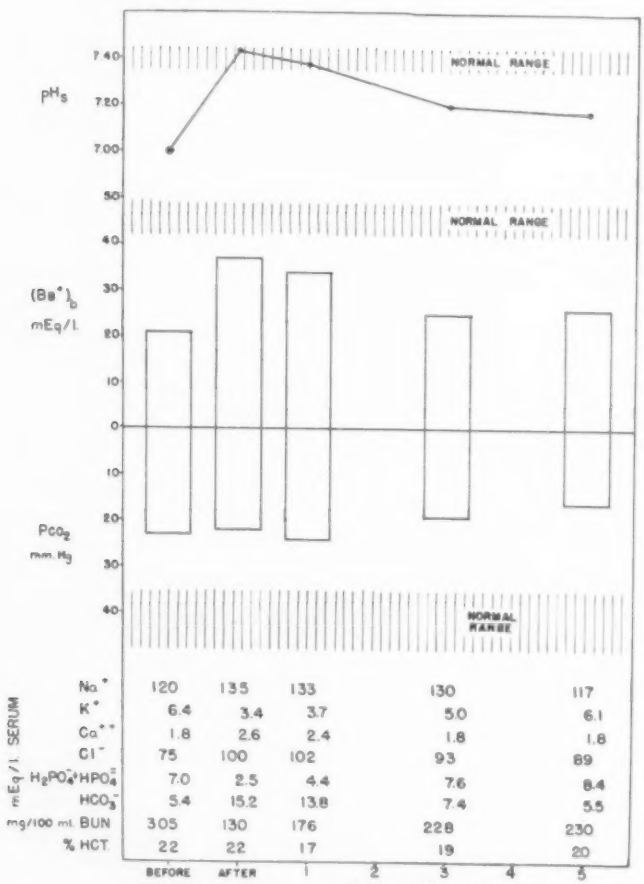

Fig. 5.—The determined and derived values of patient D.D.

The 24-hour urine volume averaged 200 ml. Figure 4 shows the chemical changes resulting from, and subsequent to, dialysis. In this instance the acid-base balance showed a much more rapid rate of return toward the predialysis state. Although the patient showed an increased ability to tolerate oral fluids 2 days following dialysis and expressed a subjective feeling of improvement, his clinical course continued to deteriorate, and he died 4 days after the end of this study.

CASE 5. D.D., a 56-year-old man, had chronic pyelonephritis. A left nephrectomy had been performed 33 years ago. Two years before admission he had a myocardial infarction. For 6 months he had noted weight loss, increasing fatigue, nausea, and vomiting. He was hospitalized and treated with intravenous fluids without improvement. On transfer to this hospital physical examination showed a semi-stuporous patient with a blood pressure of 130/70 mm. Hg. Cardiomegaly was present. Urinalysis disclosed 3+ protein and many white and red cells. Stool was

4+ on guaiac test. The serum protein was 7.2 gm. per 100 ml. The 24-hour urine output averaged 400 ml. The changes in the acid-base balance and serum electrolytes following dialysis are shown in Fig. 5. It can be seen that the regression of the acidosis toward the predialysis state was quite rapid. Although the patient ceased vomiting on the second postdialysis day and was able to take oral fluids, he remained oliguric, his clinical condition deteriorated, and he died on the sixth day following dialysis.

Discussion. The acid-base balance and serum electrolytes of 5 patients with varying degrees of chronic renal insufficiency have been studied following hemodialysis. All patients were severely "acidotic" prior to dialysis, having serum pH values ranging from 6.95 to 7.14. Hemodialysis alleviated this acidosis and the serum pH returned to normal or nearly normal values. In the first 3 cases the serum pH during the postdialysis period showed little tendency to revert to predialysis levels; in the last 2 cases it showed a more rapid fall. Thus these changes in the serum pH correlated well with the clinical course during the postdialysis period.

The acidosis present in all of these patients was of the metabolic type as evidenced by the decreased whole blood buffer base. The buffer base concentration was returned toward normal levels by hemodialysis. Following dialysis it was well maintained in the first 3 cases, but in the last 2 cases the concentration of buffer base rapidly diminished. This increase in buffer base during dialysis resulted primarily from the increase in the serum bicarbonate ion concentration. Although this increase was well maintained in the first 3 cases, the bicarbonate concentration rapidly decreased in the last 2 cases. These changes in the buffer base due to the alterations in its bicarbonate fraction correlated as well as did the pH with the clinical course of the patients.

A metabolic acidosis may be associated with either a total base deficit or a fixed acid excess. Three of these patients (E.M., H.H., and D.D.) had a significantly decreased total serum cation concentration prior to dialysis as evidenced by a decrease in its major component, the serum sodium. Hemodialysis raised the sodium and total base concentration toward normal in these patients. Patients H.H. and D.D., however, had a rapid lowering of the serum sodium concentration following dialysis to predialysis levels. The other patients maintained a normal total base concentration during the postdialysis period.

Prior to dialysis only one patient (G.T.) had a fixed acid excess. This was associated with hyperchloremia which was corrected by dialysis. Two patients (H.H. and D.D.) prior to dialysis had a normal "fixed acid" concentration which was associated with a marked hypochloremia; the nonchloride fixed acids being greatly increased. Dialysis lowered the concentration of nonchloride fixed acids and corrected the hypochloremia which however, reappeared in the postdialysis period. Hypochloremia also occurred postdialysis in Case 2 (E.M.).

This study has verified the fact that the clinical improvement of chronically ill patients having the uremic syndrome does not occur until about 48 hours after dialysis during which period of time no rapid changes are occurring in either acid-base relationships or serum electrolyte concentrations. It has been postulated that this period of time is necessary for adjustment in intracellular metabolism (Weller, Swan and Merrill[15]). Since chronic renal failure represents a slowly developing abnormality of both extracellular and intracellular composition this is not

surprising. One of the characteristic defects of chronic uremia is acidosis as a result of the inability to excrete hydrogen ion which results from ordinary metabolic processes. The effect of increasing hydrogen ion concentration upon enzyme activity and metabolic processes is a universal phenomenon which may well explain many of the physiologic abnormalities of uremia. It was pointed out many years ago that a large part of the neutralization of administered acids is done by tissue buffers (Haldane[4], Van Slyke and Cullen[13]). More recent studies with acid loading of normal subjects suggests that ¾ of the retained hydrogen ion is buffered by intracellular fluid and bone (Schwartz, Jenson and Relman[10], Swan and Pitts[12]). This is a slower process and one which may not be readily apparent from analyses of extracellular fluid. The results obtained in our experiments suggest that intracellular changes of which intracellular buffering of hydrogen ion must be one of the most important may account for the clinical phenomenon. In any case it is apparent that none of the measured extracellular parameters correlate with the delayed clinical improvement.

Summary. The acid-base changes in 5 uremic patients have been studied during and following hemodialysis. All patients initially showed a metabolic acidosis with a decreased buffer base concentration. This returned toward normal during dialysis primarily because of an increase in the bicarbonate fraction. These immediate chemical changes did not correlate with the delay in onset of clinical improvement. However, the 3 patients who maintained their improved acid-base status in the postdialysis period also maintained their clinical improvement, while the 2 patients having a rapid reappearance of their metabolic acidosis showed rapid clinical deterioration.

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(Interlingua on page 624)

SERENDIPITY IN THE DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM*

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"Serendipity" is an unfamiliar word but it does appear in most unabridged dictionaries. It means the ability to find valuable things unexpectedly and is derived from a fairy tale, "The Three Princes of Serendip," the heroes of which were continually finding valuable things by chance. The word was coined by Horace Walpole, the fourth Earl of Oxford, and its usage in connection with medical research was initiated by the late Walter B. Cannon[2]. Dr. Cannon used it to characterize the not infrequent valuable scientific discoveries which have been made by chance during the course of entirely irrelevant experimental observations. Up to the present time little emphasis has been given to the role of serendipity in clinical diagnosis. Perhaps nowhere in the practice of medicine is this faculty more helpful than in the recognition of primary hyperparathyroidism.

The physician usually suspects the presence of primary hyperparathyroidism when he encounters signs and symptoms of skeletal disease or renal calculi. If he be astute enough, he may think of the diagnosis in the presence of symptoms attributable to hypercalcemia *per se*, especially when the concentration of calcium in the serum is substantially elevated. Even in the absence of such signs and symptoms, the clinician occasionally may stumble on the diagnosis as illustrated by the 20 cases reported in this paper. The value of serum calcium for each patient was significantly elevated and returned to normal after the removal of abnormal parathyroid tissue.

Inasmuch as the diagnosis of primary hyperthyroidism is almost totally dependent on laboratory data, it should be mentioned that the accepted range of normal values for serum calcium and phosphorus varies considerably from laboratory to laboratory. In our laboratories the range of normal values for calcium is estimated to be 9.2 to 10.4 mg. per 100 ml. of serum and that for inorganic phosphorus (hereinafter referred to as "phosphorus") to be 2.5 to 4.5 mg. per 100 ml. of serum. The concentration of serum calcium is determined by a modification of the method of Clark and Collip[3] and that of phosphorus is determined by the method of Power[7].

*Read at the meeting of the Association of American Physicians, Atlantic City, New Jersey, May 6 and 7, 1958. An abbreviation of this paper will appear in the Transactions of the Association of American Physicians for 1958.

†The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

TABLE 1.—SERENDIPITY IN THE DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM

Case	Age (yr.), sex	Circumstances leading to diagnosis of primary hyperparathyroidism	Values in serum; mg./100 ml. Before operation* Calcium	Before operation* Phosphorus	After operation Calcium	After operation Phosphorus	Parathyroid lesion found at operation
		Surgical procedure					
1	40F	Carcinoma of thyroid	11.4	2.5	9.1	3.3	1.5 cm. chief and transitional water-clear cell adenoma
2	39F	Nontoxic adenomatous goiter	11.7	2.7	9.2	3.6	900 mg. transitional water-clear cell adenoma
3	70F	Toxic adenomatous goiter	11.6	2.8	9.6	3.9	460 mg. chief cell adenoma
4	57F	Pharyngo-esophageal diverticulum	11.7	1.8	9.6	3.3	Wasserhelle hyperplasia
		Neurologic complaint					
5	18M	Grand mal seizures	14.7	2.2	10.0	3.4	300 mg. chief cell adenoma
6	34F	Episodes of unconsciousness	12.7	2.3	12.2†	2.7	Multiple adenomatosis

*Single determination in cases 1, 2 and 3; mean value of 2 to 5 determinations in all other cases.

6	34F	Episodes of unconsciousness	12.7	2.3	12.2†	2.7	Multiple adenomatosis
7	50F	Episodes of unconsciousness	12.9	2.3	11.9†	3.0	Multiple adenomatosis
8	64F	Headaches	10.9	3.4	9.9	4.0	340 mg. chief and transitional water-clear cell adenoma
9	46F	Brain tumor(?)	15.8	5.3‡	10.1	3.6	2 cm. chief and transitional water-clear cell adenoma
		Backache					
10	35F	Lumbar disk	14.9	1.6	9.7	3.1	1270 mg. chief and transitional water-clear cell adenoma
11	55M	Lumbar disk	11.8	2.6	9.2	3.2	2 cm. chief and transitional water-clear cell adenoma
12	44F	Coccygodynia	10.7	1.9	9.2	2.8	560 mg. oxyphil cell adenoma
		Miscellaneous conditions					
13	44F	Hypertension	10.9	2.4	9.9	3.7	250 mg. chief cell adenoma

TABLE 1.—SERENDIPITY IN THE DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM (*Continued*)

Case	Age (yr.), sex	Circumstances leading to diagnosis of primary hyperparathyroidism	Values in serum; mg./100 ml. Before operation* Calcium	Before operation* Phosphorus	After operation Calcium	After operation Phosphorus	Parathyroid lesion found at operation
14	54F	Belching and malaise	15.4	3.7‡	9.8	3.2	7000 mg. transitional water-clear cell adenoma
15	62F	Tightness of throat	11.0	2.8	6.9	2.5	410 mg. chief cell adenoma
16	62F	Pseudohypoparathyroidism (?)	11.3	2.5	9.0	3.5	1500 mg. transitional water-clear cell adenoma
17	11F	Ectodermal dysplasia	13.0	2.9	10.1	4.2	120 mg. chief cell adenoma
18	55F	Paresthesias	11.0	2.8	9.6	3.5	100 mg. chief cell adenoma
19	63F	Cramps in feet	12.6	1.9	9.4	3.4	300 mg. chief and transitional water-clear cell adenoma
20	52F	Twitching when falling asleep	11.8	2.3	9.6	3.7	2000 mg. chief cell adenoma

†Patient believed to have additional hyperfunctioning parathyroid tissue. See text.
‡Azotemia present.

The relevant data on our 20 patients are shown in the accompanying table. There were 2 males and 18 females. One patient had wasserhelle hyperplasia of the parathyroid glands, 2 patients had adenomatosis of the parathyroids associated with adenomas of other endocrine glands, and each of the remaining 17 patients had a solitary parathyroid adenoma.

Report of Cases. HYPERPARATHYROIDISM DISCOVERED INCIDENTALLY DURING OPERATION FOR OTHER CONDITIONS. In cases 1, 2, and 3 unsuspected parathyroid tumors were discovered during operation for disorders of the thyroid. In case 4, wasserhelle hyperplasia was discovered during the removal of a pharyngo-esophageal diverticulum.

Case 1 (Carcinoma of Thyroid). A 40-year-old woman, first seen at the Mayo Clinic in 1944 at the age of 30 years, had numerous complaints which were thought to be of psychoneurotic origin. In 1945 a portion of the right breast involved by chronic cystic mastitis was excised. In 1954 a small nodule in the right lobe of the thyroid and a questionable nodule in the left lobe were palpated. Because of the small size of the nodules and the patient's psychologic disorder, surgical treatment was deferred until 6 months later. Microscopic examination of the nodule in the right lobe of the thyroid showed grade-1 papillary and follicular adenocarcinoma. The remainder of the right lobe was removed and showed colloid thyroid. Metastasis was not present and the left lobe of the thyroid was normal.

During operation a parathyroid adenoma measuring 1.5 by 0.5 by 0.5 cm. and consisting of chief and transitional water-clear cells was found in the usual position of the right inferior parathyroid gland. A sample of the patient's blood was obtained during the operation; the value of calcium was 11.4 mg. and that of phosphorus was 2.5 mg. per 100 ml. of serum. Two days after operation the serum calcium measured 8.2 mg. and phosphorus 2.6 mg. per 100 ml. On the tenth postoperative day the serum calcium measured 9.1 mg. and phosphorus, 3.3 mg. The values of serum calcium and phosphorus were found to be normal on several occasions during the next 2 years. Careful questioning of the patient after surgical intervention revealed a history of renal colic and the passage of a stone in the spring of 1949. Subsequent roentgenographic review of the skeleton and an excretory urogram did not disclose any abnormality.

COMMENT. Retrospectively, the only symptom that could be attributed to the hyperparathyroidism was the renal colic present in 1949. Since operation, the psychoneurotic symptoms previously described have persisted unchanged.

The coexistence of primary hyperparathyroidism and carcinoma of the thyroid is relatively uncommon. Ogburn and Black[6] in 1956 observed this combination in 4 of 230 cases of primary hyperparathyroidism. The foregoing case is case 3 in their report.

Case 2 (Nontoxic Adenomatous Goiter). A 39-year-old woman came to the Mayo Clinic in October, 1953, because of a goiter which she had had for 9 years. For 1 year she had noted occasional feelings of pressure on her windpipe; she had had some dyspnea but no stridor. On examination she was found to have a large adenomatous goiter. The basal metabolic rate was plus 5. At operation the thyroid was found to be 3 to 4 times the normal size and consisted of multiple, degenerating fetal colloid adenomas in a colloid thyroid. An incidental finding during operation was a 900-mg. parathyroid adenoma in the usual position of the left inferior parathyroid. It was composed of transitional water-clear cells. A sample of the patient's blood was obtained during operation and the values of calcium and phosphorus were 11.7 mg. and 2.8 mg. per 100 ml. of serum respectively. Thirteen days after operation the value of serum calcium was 9.2 mg. and that of phosphorus was 3.6 mg. per 100 ml. Roentgenograms of the lumbar portion of the spinal column, and of the kidneys, ureters, and bladder did not show evidence of any abnormality.

COMMENT. In retrospect, there were no symptoms or complications attributable to hyperparathyroidism, which must be regarded as having been entirely asymptomatic.

Case 3 (Toxic Adenomatous Goiter). A 70-year-old woman came to the Mayo Clinic in August, 1956, because of nervousness of 9 months' duration. During this time she had had tremor, insomnia, fatigue and weakness; she had lost 50 pounds, but intolerance to heat or increased sweating had not developed. She had had a goiter since the age of 20 years, but she did not think it had enlarged. On physical examination she appeared to be hyperthyroid and was found to have a large adenomatous goiter with substernal extension. The basal metabolic rate was plus 34; the value of protein-bound iodine was 21.3 μg., and that of butanol-extractable iodine was 14.4 μg. per 100 ml. of serum. At operation 190 gm. of adenomatous and colloid thyroid tissue was removed. In the usual region of the left superior parathyroid there was a parathyroid adenoma composed of chief cells and weighing 460 mg. A sample of the patient's blood drawn during operation contained 11.6 mg. of calcium and 2.7 mg. of phosphorus per 100 ml. of serum. Two days after operation the value of serum calcium was 8.2 mg. and that of phosphorus, 3.0 mg. per 100 ml. Determinations 1½ weeks and 3½ months after operation showed the values of serum calcium to be 10.4 and 9.6 mg. and of phosphorus, 3.0 and 3.9 mg. per 100 ml., respectively. No roentgenograms of the kidneys or bones were made.

COMMENT. This case raises the interesting question as to whether the hypercalcemia was due to primary hyperparathyroidism or hyperthyroidism. Since the patient had a toxic adenomatous goiter rather than Graves disease, and because of the postoperative changes in the serum phosphorus, we are of the opinion that this case is one of coexisting primary hyperparathyroidism and hyperthyroidism. Four cases of hypercalcemia secondary to hyperthyroidism have been reported by Koenig, Scholz and Salassa[5]. All 4 patients had parenchymatous hypertrophy (Graves' disease) rather than toxic adenomatous goiter and in none did the value of serum phosphorus change significantly after operation.

Case 4 (Pharyngo-esophageal Diverticulum). A 57-year-old woman came to the Mayo Clinic in September, 1955, because for 2 years she had had difficulty in swallowing. Roentgenograms of the esophagus revealed a moderately large pharyngo-esophageal diverticulum lying to the left of the midline of the esophagus. During surgical removal of the diverticulum a firm mass was noted posterior to the esophagus and attached to the thyroid. This was excised and microscopic examination showed it to be wasserhelle hyperplasia of a parathyroid gland. Postoperatively several determinations of the serum calcium showed values of 11.1, 12.2, 12.1, and 11.3 mg. per 100 ml. Simultaneous values of serum phosphorus were 1.5, 2.5, 1.5, and 1.9 mg. per 100 ml. Eight weeks after the first operation an exploration of the neck was performed. The right inferior parathyroid was subtotally resected, with 6 gm. of tissue being removed and approximately 100 mg. of tissue being left in place. The right superior parathyroid was totally resected and weighed 200 mg. Parathyroid tissue was not found in the usual sites of the 2 left parathyroids and it was thought that the tissue excised at the initial operation probably represented a fusion of both left parathyroids. Examination of the parathyroid tissue showed wasserhelle hyperplasia. Adequate parathyroid tissue was removed because 3 days after surgical intervention the value of calcium was 9.1 and that for phosphorus was 3.2 mg. per 100 ml. of serum. Six months after operation the calcium measured 9.6 mg. and phosphorus, 3.3 mg. per 100 ml. No studies of the skeleton or urinary tract were done.

HYPERPARATHYROIDISM DISCOVERED DURING INVESTIGATION OF NEUROLOGIC COMPLAINTS. In cases 5, 6, and 7 the concentration of calcium in the serum was determined in order to rule out hypocalcemia as a possible cause of convulsions or spells of unconsciousness. In each instance hypercalcemia and, subsequently, a parathyroid tumor were found. In cases 8 and 9 evidence of demineralization of the bones was incidentally noted in roentgenograms of the head. Investigation of this finding ultimately led to the diagnosis of hyperparathyroidism and the removal of a parathyroid tumor.

Case 5 (Grand Mal Seizures). An 18-year-old boy came to the Mayo Clinic in April,

1946, because of a convulsive disorder of 5 years' duration. To rule out the possibility of hypocalcemia as the cause of the convulsions, the concentration of calcium in the serum was determined and was found to be 13.5 mg. per 100 ml. Subsequent values of the serum calcium were 13.1, 15.1, 16.1, and 15.0 mg.; corresponding values of phosphorus were 2.2, 2.2, 2.1, and 2.4 mg. per 100 ml. of serum. The value of alkaline phosphatase was 6.8 Bodansky units per 100 ml. of serum. Roentgenograms of the skull, hands, and lumbar portion of the spinal column showed evidence of slight demineralization. An electroencephalogram showed a generalized dysrhythmia. Roentgenograms of the kidneys, ureters, and bladder did not show evidence of any abnormality. An exploration of the parathyroids was advised and at operation a parathyroid adenoma weighing 300 mg. was found in the usual region of the left inferior parathyroid. This consisted of chief cells. On the third postoperative day the serum calcium measured 10.0 mg. and phosphorus, 3.4 mg. per 100 ml.

Retrospective questioning revealed that the patient had had some weakness, fatigue, polyuria, and polydipsia. Removal of the parathyroid tumor did not appear to influence the patient's seizures, which were diagnosed as an idiopathic convulsive disorder. A letter from another hospital in February, 1947, revealed that the patient had been hospitalized there and that a diagnosis of status epilepticus had been made.

COMMENT. Although the hyperparathyroidism was discovered by chance, a review of the patient's history after the diagnosis had been established brought to light symptoms which may be associated with hypercalcemia; namely, weakness, fatigue, polyuria, and polydipsia. It is not known whether the weakness and fatigue eventually disappeared, but polyuria or polydipsia was not noted while the patient was hospitalized. The elevated concentration of alkaline phosphatase and the roentgenologic findings suggest that there was some skeletal involvement.

Case 6 (Episodes of Unconsciousness and Multiple Endocrine Adenomatosis). A woman, 34 years of age, first came to the Mayo Clinic in September, 1943, because of episodes manifested by blurring of vision and, at times, numbness and tingling of the right leg. On several occasions she had lost consciousness for 1 to 2 hours and on other occasions she felt as though she were in a trance. These episodes were shortened by eating sweets. Although the episodes were thought to represent hypoglycemia, the concentration of serum calcium was determined to rule out hypocalcemia. The value of calcium was 12.1 mg. per 100 ml. of serum. Subsequent determinations showed values of calcium to be 13.6 and 12.4 mg., and of phosphorus, 2.5 and 2.1 mg. per 100 ml. To establish a diagnosis of hyperinsulinism the patient was fasted and after 26 hours, she exhibited unusual behavior and slightly slurred speech. At that time the value of blood sugar was 29 mg. per 100 ml.

In September, 1943, an exploration of the pancreas was undertaken and an islet cell adenoma, 1.5 cm. in diameter, was removed. Three weeks later the patient had an episode similar to those noted prior to operation, and studies showed that she still had definite hypoglycemia. In April, 1944, the distal third of the pancreas was removed, and an islet cell adenoma, 1.5 cm. in diameter, was found in the resected tissue. In the immediate postoperative period, the patient had mild hyperglycemia and glycosuria for several days. Following this she had no further symptoms and the blood sugar was found to be normal on all subsequent examinations.

An exploration of the parathyroids was performed in February, 1945, and a parathyroid adenoma, 1 cm. in diameter, was found in the usual region of the right inferior parathyroid. Histologically this was composed of small chief cells and transitional water-clear cells. The other parathyroids were not identified during operation. On the sixth postoperative day the value of serum calcium was 10.1 and that of phosphorus was 2.3 mg. per 100 ml. However, 3 days later the value of calcium had risen to 11.4 mg. and that of phosphorus to 2.5 mg. per 100 ml. On subsequent examinations in June, 1945, September, 1946, September, 1947, and August, 1956, the values of serum calcium and phosphorus were in the same range noted before removal of the parathyroid adenoma. Hence, in August, 1956, a second exploration of the parathyroids was undertaken and a parathyroid adenoma measuring 3.0 by 1.5 by 1 cm. was found in the usual region of the right superior parathyroid and removed. The left superior parathyroid was

enlarged to 3 or 4 times the normal size and it, too, was removed. The left inferior parathyroid appeared to be atrophic. Since biopsy of this gland showed normal parathyroid tissue, the remainder of the gland was left in place.

Microscopic examination of all the abnormal parathyroid tissue showed it to be similar to that removed in 1945. On the sixth postoperative day the value of serum calcium was normal, being 10.1 mg. per 100 ml. However, on the ninth postoperative day the serum calcium measured 11.4 and the phosphorus 2.5 mg. per 100 ml. Several determinations over the next 3 months showed the values of both serum calcium and phosphorus to be in the preoperative range. It is assumed that the patient has additional hyperfunctioning parathyroid tissue, but to date she has not been willing to consider further exploration.

When the diagnosis of hyperparathyroidism was first made in 1943, a roentgenographic survey of the skeleton did not show evidence of demineralization, and several determinations of the serum alkaline phosphatase gave normal results. Neither stones nor nephrocalcinosis was evident in roentgenograms of the kidneys, ureters, and bladder. In 1956 evidence of skeletal disease was absent, but an excretory urogram showed 3 small stones in the right kidney and a stone in the right ureter. Also, 6 months before the latter examination, the patient had begun to have epigastric distress. Roentgenograms of the stomach and duodenum revealed evidence of a duodenal ulcer.

COMMENT. In addition to the syndrome of multiple endocrine adenomatosis, which will be commented on after the report of case 7, this case is of particular interest because the patient was observed to have had asymptomatic hyperparathyroidism for more than 12 years before renal complications developed. When the patient was first seen in 1943 there was no evidence of skeletal or renal disease. However, by 1956 stones had developed in the urinary tract. In addition, the patient had a duodenal ulcer, a condition commonly associated with hyperparathyroidism (St. Goar[8]).

Case 7 (Episodes of Unconsciousness and Multiple Endocrine Adenomatosis). A 50-year-old woman came to the Mayo Clinic in March, 1947, because of a duodenal ulcer of 2 years' duration. For 23 years she had had episodes of blurring of vision, weakness, and tremor, and on several occasions had become unconscious. On examination she had features suggestive of acromegaly and roentgenograms of the head showed evidence of a pituitary tumor. A presumptive diagnosis of hypoglycemia secondary to a hyperfunctioning islet cell adenoma was made, but in order to rule out the possibility of hypocalcemia as an explanation for her spells, the concentration of serum calcium was determined. Successive values of serum calcium were 13.8, 12.5, and 12.3 mg. and concomitant values of serum phosphorus were 2.2, 2.4, and 2.0 mg. per 100 ml.

Since a medical regimen failed to alleviate the patient's symptoms of ulcer, subtotal gastrectomy was performed on April 9, 1947. The pancreas was explored during the operation, but no islet cell adenomas were found. Exploration of the parathyroids was performed on June 3, 1947, and the surgeon resected 3 adenomatous glands which were histologically similar to those noted in case 6. On the fourth postoperative day the values of calcium and phosphorus were 8.4 and 3.3 mg. per 100 ml. of serum respectively. Although 3 months later the values of serum calcium and phosphorus were still within the normal range, a year and a half after surgical intervention, the value of calcium was 10.9 mg. and that of phosphorus was 3.3 mg. per 100 ml. of serum. Ten years after parathyroidectomy the respective values of calcium and phosphorus were 11.9 and 3.0 mg. per 100 ml. of serum. Hence, it is thought that in this case additional hyperfunctioning parathyroid tissue has grown. At no time has any evidence of skeletal disease or disease of the urinary tract been found.

Because the patient continued to have symptoms of hypoglycemia and because repeated determinations of fasting blood sugars were in the range of 30 to 40 mg. per 100 ml., the tail and a portion of the body of the pancreas were removed in 1953, but no islet cell adenomas were found. The patient has continued to have symptoms of hypoglycemia, and the presence of hyperfunctioning pancreatic islet tissue is still suspected, although, as yet, none has been found despite 2 surgical explorations of the pancreas.

COMMENT. Cases 6 and 7 have been reported more extensively as cases 1 and 3, respectively, by Underdahl

Woolner, and Black[9] in their paper on multiple endocrine adenomas. Now that the syndrome of multiple endocrine adenomatosis has become more clearly defined, it is evident that the diagnosis of such cases can be facilitated if the clinician will determine the value for serum calcium in all patients with hyperfunctioning islet cell adenomas of the pancreas. It is of interest that elevated concentrations of serum calcium have developed in both of these patients despite transient remission following the removal of several adenomatous parathyroids. This tendency for hyperparathyroidism to recur or persist may be characteristic of multiple endocrine adenomatosis, but it has not been seen in simple parathyroid adenomas.

Case 8 (Headaches). A 64-year-old woman was first seen at the Mayo Clinic in 1941 at the age of 52 years, at which time she was found to have a duodenal ulcer. In 1951 partial gastrectomy and duodenectomy were done. She was next seen in January, 1953, because of headaches. The only abnormality evident on roentgenograms of the skull was demineralization. Investigation of the demineralization showed the following values: calcium, 10.8 and 10.9 mg.; phosphorus, 3.3 and 3.3 mg.; and alkaline phosphatase, 3.9 Bodansky units, all per 100 ml. of serum. The patient was unable to remain for further studies but returned in July, 1953. At that time the calcium measured 10.7 and 11.1 mg., the phosphorus 3.5 and 3.5 mg., and the alkaline phosphatase 11.4 King and Armstrong units per 100 ml. of serum. Surgical exploration of the parathyroids was performed and an adenoma, weighing 340 mg. and composed of chief and transitional water-clear cells, was found in the usual position of the right inferior parathyroid. Roentgenograms of the renal regions did not show evidence of stones or nephrocalcinosis. Several determinations of the concentrations of serum calcium and phosphorus were made over the next 4 years and all were within normal limits. In May, 1957, the serum calcium measured 9.9 and phosphorus, 4.0 mg. per 100 ml. Roentgenograms of the skull again showed evidence of demineralization.

COMMENT. Although investigation of demineralization of the skull led to the diagnosis of hyperparathyroidism, it is probable that this change represents osteoporosis rather than demineralization associated with hyperparathyroidism, even though demineralization was present in the hands and thoracic portion of the spinal column. The normal concentrations of alkaline phosphatase prior to operation and the persistence of demineralization as long as 4 years after surgical correction of the hyperparathyroidism suggest that the patient actually had osteoporosis. What relation her duodenal ulcer bore to the hyperparathyroidism is open to speculation.

Case 9 (Question of Brain Tumor). A woman, 46 years of age, came to the Mayo Clinic in May, 1956, because of pain in her back and because she had been told by an osteopathic physician that she might have a brain tumor. The blood pressure was 190 mm. Hg systolic and 110 mm. diastolic. Roentgenograms of the lumbar portion of the spinal column were interpreted as showing evidence of hypertrophic changes, but roentgenograms of the skull and right hand showed evidence of demineralization suggestive of hyperparathyroidism. Roentgenograms of the kidneys, ureters, and bladder did not show evidence of stones or nephrocalcinosis. Values of calcium were 16.2, 16.3, and 14.8 mg. and of phosphorus, 4.5, 5.2, and 6.3 mg. per 100 ml. of serum. Alkaline phosphatase measured 15.6 King and Armstrong units per 100 ml. of serum, and urea measured 92 mg. per 100 ml. of blood. Exploration of the parathyroids disclosed a parathyroid adenoma 2 cm. in diameter. This was found in the usual position of the right superior parathyroid and consisted of chief and transitional water-clear cells. On the second postoperative day the values for calcium and phosphorus were 9.9 and 4.2 mg. per 100 ml. of serum respectively. Six months later the calcium measured 10.1 and phosphorus, 3.6 mg. per 100 ml. of serum and the value of urea was 48 mg. per 100 ml. of blood. The blood pressure at that time was 210 mm. of mercury systolic and 130 mm. diastolic.

COMMENT. In this case the diagnosis of hyperparathyroidism was suggested

by the roentgenographic findings. Although plain roentgenograms of the urinary tract did not show evidence of renal involvement, some renal changes secondary to hyperparathyroidism probably had developed since the elevated value of urea found preoperatively dropped significantly after the removal of the parathyroid adenoma.

HYPERPARATHYROIDISM DISCOVERED INCIDENTALLY DURING INVESTIGATION OF BACKACHE. In cases 10, 11, and 12 unsuspected hyperparathyroidism was found during the investigation of nephrocalcinosis or renal stones, which were discovered incidentally on roentgenograms of the spinal column.

Case 10 (Lumbar Disk). A 35-year-old woman came to the Mayo Clinic in February, 1956, because of backache of 3 to 4 years' duration and sciatic pain on the left side, of 1½ years' duration. Roentgenograms of the lumbar portion of the spinal column showed evidence of bilateral nephrocalcinosis. Investigation of this finding elicited the following values: serum calcium, 14.9, 14.9, and 14.9 mg.; serum phosphorus, 2.1, 1.4, and 1.4 mg.; serum alkaline phosphatase, 14.2 King and Armstrong units, and blood urea 32 mg. per 100 ml. Further questioning of the patient disclosed that at the age of 19 years she had had an episode of pain and obstruction of the urinary tract which was relieved by cystoscopic removal of calcareous material. One month before coming to the clinic polyuria and polydipsia developed abruptly, but during her examination the urinary volume on 2 consecutive days was found to be only 1600 and 1580 ml. per 24 hours. Exploration of the parathyroids revealed a parathyroid adenoma, situated in the usual position of the left inferior parathyroid. It weighed 1270 mg. and was composed of mixed chief and transitional water-clear cells. Four days after removal of the adenoma the serum contained 9.5 mg. of calcium and 1.6 mg. of phosphorus per 100 ml.

Approximately 1 year later (early 1957) symptoms of a duodenal ulcer developed. The patient was next seen at the clinic in February, 1958. At that time the values for calcium and phosphorus were 9.7 and 3.1 mg. per 100 ml. of serum respectively; alkaline phosphatase measured 6.5 King and Armstrong units per 100 ml. of serum and urea, 34 mg. per 100 ml. of blood. Roentgenograms of the renal regions showed no evidence of change in the nephrocalcinosis; those of the stomach and duodenum showed evidence of a duodenal ulcer. The patient's blood pressure was normal each time she was examined.

COMMENT. Although the patient initially had some skeletal changes from hyperparathyroidism, as evidenced by the increased value of serum alkaline phosphatase, roentgenograms of the lumbar portion of the spinal column and right hand did not show evidence of demineralization. The backache and sciatic pain were thought to be caused by a protruded lumbar disk rather than by skeletal changes secondary to hyperparathyroidism. The patient's backache and sciatic pain continued unchanged after removal of the parathyroid adenoma and were still present when she was last seen in 1958. Inasmuch as the first symptoms referable to the duodenal ulcer appeared a year after the serum calcium had returned to normal, any connection between the hyperparathyroidism and the development of the ulcer is open to question.

Case 11 (Lumbar Disk). A 55-year-old man came to the Mayo Clinic in November, 1954, because of intermittent backache of 25 years' duration. For several months he had had right sciatic pain which led to a clinical diagnosis of ruptured intervertebral disk. Subtotal hemilaminectomy was carried out and a protruded disk was removed from the fourth lumbar interspace on the right. Roentgenograms of the lumbar portion of the spinal column prior to operation showed hypertrophic changes and bilateral renal calculi. In the course of investigating the renal calculi, the calcium measured 12.4, 11.5, and 11.6 mg.; phosphorus, 2.6, 2.8, and 2.3 mg.; the alkaline phosphatase 13.2 King and Armstrong units per 100 ml. of serum; and the blood urea, 28 mg. per 100 ml. The parathyroids were explored in December, 1954, and an adenoma, which measured 2.5 by 2.1 by 1.2 cm. and consisted of chief cells and transitional water-clear cells, was found in the usual position of the right superior para-

thyroid. Several days after surgical treatment the value of calcium was 9.2 and that of phosphorus was 3.0 mg. per 100 ml. of serum. Six months later a stone composed of calcium oxalate was extracted from the right ureter. The serum calcium at that time measured 9.3 and phosphorus, 2.5 mg. per 100 ml.

Case 12 (Coccygodynia). A woman, 44 years of age, came to the Mayo Clinic in December, 1951, because of a goiter which had been noted 3 months previously. Increase in the size of the goiter was blamed for a feeling of tightness at the base of the neck. The patient requested that her coccyx also be examined because of pain which had followed a fall 2 years before. Roentgenograms of the lumbar portion of the spinal column and coccyx were without evidence of abnormality but incidentally showed a stone in the lower pole of the left kidney. On investigation of this finding the value of calcium was found to be 10.6 and 10.8 mg.; phosphorus, 1.8 and 1.9 mg. and alkaline phosphatase, 3.3 Bodansky units each per 100 ml. of serum. The patient was given a diet containing 135 mg. of calcium per day for 3 days during which time the urinary excretion of calcium measured 221, 285, and 223 mg., and the excretion of phosphorus, 626, 586, and 554 mg. per 24 hours. The basal metabolic rate was minus 8. At operation the patient was found to have a simple colloid and adenomatous goiter. In the usual position of the right superior parathyroid gland there was a parathyroid adenoma, which weighed 560 mg. and was composed of oxyphil cells. Two days after operation the value for calcium was 7.9 and of phosphorus, 4.6 mg., but 2 weeks later calcium measured 9.2 and phosphorus, 2.8 mg. per 100 ml. of serum. During the postoperative period the patient spontaneously passed the stone from the left kidney.

COMMENT. In this instance there were 2 opportunities for the parathyroid adenoma to be found. The first was the discovery of the renal stone, which ultimately led to the diagnosis of hyperparathyroidism. However, even if the diagnosis had not been made preoperatively, the surgeon presumably would have found the tumor during the removal of the goiter.

MISCELLANEOUS CONDITION LEADING TO THE DIAGNOSIS OF HYPERPARATHYROIDISM.

Case 13 (Hypertension). A 44-year-old woman came to the Mayo Clinic in January, 1958, because of joint symptoms which were ultimately considered to be due to mild rheumatoid arthritis. During her examination the blood pressure was 196 mm. Hg systolic and 110 mm. diastolic. An intravenous urogram which was obtained to evaluate the hypertension showed evidence of bilateral nephrocalcinosis. The values of calcium, which were obtained on this account, were 11.4, 10.8, 10.6, and 10.8 mg. per 100 ml. of serum; corresponding values of phosphorus were 2.6, 2.3, 2.4, and 2.3 mg., that of alkaline phosphatase, 7.2 King and Armstrong units, per 100 ml. of serum. The value of urea was 34 mg. per 100 ml. of blood. An exploration of the parathyroids was advised and a 250-mg. chief cell adenoma was found in the usual position of the left inferior parathyroid. Seven days after operation the value of serum calcium was 9.9 and that of phosphorus was 3.7 mg. per 100 ml. No evidence of skeletal disease was noted on the excretory urogram or the roentgenograms of the skull and other bones.

COMMENT. Cases 10, 11, 12, and 13 demonstrate that an investigation of the cause of nephrocalcinosis or renal calculi may be rewarding even when these conditions are asymptomatic or are encountered accidentally.

Case 14 (Belching and Malaise). In August, 1953, a 54-year-old woman came to the Mayo Clinic because of anemia. Two to 3 years before she began to have epigastric gas and belching, and on examination elsewhere in November, 1952, she had been found to be anemic. In the 10 months before coming to the clinic she had had considerable nausea and vomiting and had lost 24 pounds. When she went without food for 2 to 3 hours she had a hungry feeling, which was relieved by ingestion of milk or food.

The concentration of hemoglobin measured 11.2 gm. per 100 ml. of blood; the erythrocyte count was 3,600,000 and the leukocyte count, 10,200 per c.mm. of blood. A blood smear showed some hypochromasia, polychromasia, and rouleau formation. Roentgenograms of the gallbladder showed a normally functioning gallbladder without stones and nephrocalcinosis of the right kidney. Roentgenograms of the esophagus, stomach and duodenum and colon were normal. However, the roentgenograms of the colon incidentally revealed significant demineralization of the spinal column sugges-

tive of hyperparathyroidism. Roentgenograms of the thorax showed evidence of a cystic lesion in the seventh right rib, and those of the skull and hands showed typical changes of hyperparathyroidism. Successive values of calcium were 15.6 and 15.1 mg. per 100 ml. of serum. Other values were as follows: 3.7 and 3.7 mg. of phosphorus, and 23.2 Bodansky units of alkaline phosphatase per 100 ml. of serum, and 84 mg. of urea per 100 ml. of blood.

On exploration a parathyroid adenoma, weighing 7 gm. and composed of transitional water-clear cells, was found in the usual position of the right inferior parathyroid. Two days after operation symptoms of hypocalcemia developed, and the value of calcium was 7.1 and that of phosphorus, 2.6 mg. per 100 ml. of serum. The patient was given vitamin D and calcium lactate for the next 3 months. One year after operation the values of serum calcium and phosphorus were 9.8 and 3.2 mg. respectively, and the value of urea was 78 mg. per 100 ml. of blood. The concentration of hemoglobin was 11.7 gm. per 100 ml. of blood and erythrocytes numbered 4,150,000 per c.mm. of blood. The blood pressure was normal at each examination.

COMMENT. In retrospect, it is probable that the patient's nausea, vomiting, and malaise were caused by the hypercalcemia *per se*, since they subsided following removal of the parathyroid adenoma. Hence, the diagnosis might have been suspected prior to roentgenographic examination of the gastrointestinal tract which revealed 2 additional clues to the diagnosis; namely, nephrocalcinosis and demineralization of the skeleton.

Case 15 (Tightness of the Throat). A 62-year-old woman came to the Mayo Clinic in August, 1954, because for 1 year she had experienced sensations of pulling, tugging, and tightness in her throat. She had had a thyroidectomy at the clinic in 1917 for an exophthalmic goiter; her convalescence was uneventful. In 1954 the value of serum calcium was determined to rule out the possibility of hypoparathyroidism as a cause of her symptoms. Two determinations showed values of calcium to be 11.0 and 11.0 mg. per 100 ml. of serum. The serum phosphorus measured 2.8 mg. and the serum alkaline phosphatase measured 12 King and Armstrong units per 100 ml. of serum. On exploration of the parathyroids a chief cell adenoma weighing 410 mg. was found in the usual position of the left inferior parathyroid. The day after operation the value of serum calcium was 8.7 and of phosphorus, 3.1 mg. per 100 ml.; 3 days later the values were 6.9 and 2.5 mg. respectively. The patient was given calcium lactate orally because she had mild symptoms of hypocalcemia.

Case 16 (Question of Pseudohypoparathyroidism). In June, 1955, a 62-year-old woman came to the Mayo Clinic because of choking spells of 5 or 6 years' duration. She had had a goiter for at least 5 years but did not think it was enlarging. On examination she was found to have a multinodular goiter which seemed to be 2 to 3 times the normal size. She was also found to have short fourth metacarpals bilaterally. To rule out the possibility of pseudohypoparathyroidism the values of calcium and phosphorus were obtained and found to be respectively 11.3 and 2.1 mg. per 100 ml. of serum. Subsequent determinations showed values of calcium to be 11.3 and 11.4 mg.; of phosphorus, 2.8 and 2.7 mg.; and the value of alkaline phosphatase, 12 King and Armstrong units per 100 ml. of serum. At operation the thyroid was enlarged 2 to 3 times the normal size and contained multiple adenomas. A parathyroid adenoma weighing 1.5 gm. was found in the usual position of the left inferior parathyroid. This consisted of transitional water-clear cells. The day after operation the value of serum calcium was 8.4 and of phosphorus, 2.7 mg. per 100 ml. On the seventh postoperative day the values were 8.0 and 3.9 mg. per 100 ml. of serum respectively. Since the patient had no symptoms of hypocalcemia, she was not treated; 3 months later the serum calcium measured 9.0 and phosphorus, 3.5 mg. per 100 ml. Roentgenograms of the kidneys, ureters, and bladder prior to operation did not show evidence of nephrocalcinosis or renal calculi. Some osteoporosis of the spinal column was apparent, but roentgenograms of the head did not show evidence of demineralization. This patient was not considered to have renal or skeletal complications of hyperparathyroidism.

COMMENT. The discovery of hyperparathyroidism in this case was strictly fortuitous. However, had surgical treatment been advised for removal of the goiter, the tumor might have been found by the surgeon.

Case 17 (Ectodermal Dysplasia). An 11-year-old girl came to the Mayo Clinic in July, 1957, because 6 years earlier she had begun to lose some of the hair on her head. Each spring she would lose some of her hair and it would gradually grow back, only to be lost again the following spring. One year before she had lost her left eyebrow and recently she had begun to lose her right eyebrow. Also, for 1 year she had had denting, striations, and flaking of the fingernails. The pediatrician who saw her wished to exclude ectodermal dysplasia associated with hypocalcemia as an explanation for these findings. However, calcium measured 13.1, 13.0, and 12.8 mg. and phosphorus, 2.8, 2.9, and 3.1 mg. per 100 ml. of serum. The value of serum alkaline phosphatase on 2 occasions was 57.2 and 49.0 King and Armstrong units per 100 ml. Demineralization was not apparent in roentgenograms of the skull and of both hands. The parathyroids were explored and a 120-mg. chief cell adenoma was found in the usual position of the right superior parathyroid. Two days after operation the value of serum calcium was 9.5 and that of phosphorus was 3.5 mg. per 100 ml.; 8 days after operation the respective values were 10.1 and 4.2 mg.

COMMENT. This patient is the youngest ever seen at the Mayo Clinic with primary hyperparathyroidism. It is unlikely that any of her clinical signs or symptoms were related to the hyperparathyroidism.

Case 18 (Paresthesias of Hands and Feet). In January, 1958, a 55-year-old woman came to the Mayo Clinic because of tinnitus of 6 months' duration. She was thought to have Meniere's disease. During her examination she mentioned that 3 years before she had had the onset of painful swelling of the hands and, to a lesser extent, the same symptoms in her feet. These symptoms gradually subsided, but after this she began to have paresthesias of her hands, feet and the left side of her face. The concentration of serum calcium was determined to exclude hypercalcemia as the cause of the paresthesias. The values were 10.9, 11.3, 11.0, and 10.8 mg. per 100 ml. of serum. The phosphorus measured 3.0, 2.7, 3.1, and 2.6 mg. and the alkaline phosphatase, 9.5 and 11.1 King and Armstrong units, both per 100 ml. of serum. Roentgenograms of the skull did not show any abnormality. At operation a chief cell adenoma weighing 100 mg. was found in the usual position of the left inferior parathyroid. Two days subsequent to operation the values of calcium and phosphorus were 9.6 and 3.5 mg. per 100 ml. of serum respectively.

Case 19 (Nocturnal Cramps in Feet). A 63-year-old woman registered at the Mayo Clinic in August, 1957, because of constipation and foot cramps which she had had for several years. The cramps in her feet would awaken her from sleep and were relieved by placing her feet in a tub of hot water. She also thought that they were alleviated by taking calcium tablets. The amount of calcium she took is not known. After the patient had abstained from taking calcium tablets for several days, determinations of serum calcium were made. The results were as follows: 12.7, 13.2, and 12.0 mg. per 100 ml. of serum. Phosphorus measured 1.8, 1.9, and 1.9 mg. and the alkaline phosphatase, 10.1 King and Armstrong units per 100 ml. of serum. A roentgenogram of the kidneys, ureters, and bladder did not show evidence of nephrocalcinosis or calculi. Exploration of the parathyroids was performed and a 300-mg. adenoma was found in the usual position of the left inferior parathyroid. This was composed of chief and transitional water-clear cells. Two days after operation the serum calcium measured 10.2 and phosphorus 3.7 mg. per 100 ml.; 6 days later the values were 9.4 and 3.4 mg. respectively.

Case 20 (Twitching of Limbs While Falling Asleep). A 52-year-old woman came to the Mayo Clinic in June, 1956, for a general examination. She mentioned that sometimes her arms and legs twitched or jerked as she was falling asleep. She requested that the concentration of her serum calcium be measured because she had read somewhere that similar symptoms might be caused by a low concentration of calcium in the blood. Several determinations of the calcium were made and the values were 12.2, 11.6, 11.6, and 11.9 mg. per 100 ml. of serum. Corresponding values of phosphorus were 2.2, 2.4, 2.3, and 2.3 mg., and the alkaline phosphatase measured 10.1 King and Armstrong units, both per 100 ml. of serum. A plain roentgenogram of the renal regions was without abnormality. An exploration of the parathyroids was performed and a 2 gm. chief cell adenoma was found in the usual position of the right superior parathyroid. Operation was performed and 3 days later the serum calcium measured 9.4 mg. and the phosphorus, 2.5 mg. per 100 ml. Seven days after operation the values of calcium and phosphorus were 9.6 and 3.7 mg. per 100 ml. of serum.

Conclusions. These cases may be of more than passing interest and possibly of considerable importance. They comprise 6.5% of the 307 cases of surgically proved primary hyperparathyroidism that have been encountered at the Mayo Clinic. They confirm the fact suggested long ago by Albright and associates[1] that primary hyperparathyroidism, *per se*, need not produce characteristic signs or symptoms. Engel[4] has suggested the term "chemical hyperparathyroidism" if the only demonstrable abnormality is alteration in the concentrations of serum calcium and phosphorus. In retrospect at least 6 of our cases clearly fit into this category (cases 2, 6, 7, 16, 19 and 20).

It is appropriate to consider whether asymptomatic or chemical hyperparathyroidism is of any clinical importance, and why a patient exhibiting this condition should be asked to undergo an exploration of the parathyroids. Since primary hyperparathyroidism may eventually result in severe skeletal disease, severe renal disease, or both, leading in some instances to severe disability or death, we are of the opinion that it is important to the patient's welfare to remove any hyperfunctioning parathyroid tissue, even in so-called chemical or asymptomatic hyperparathyroidism. In support of this contention, case 6 in this series might be cited. This patient was first seen by us in 1943 at which time there was no evidence of skeletal or renal disease. She remained symptom-free and without discernible complications over the subsequent years, until 1956, when she was found to have renal stones and a duodenal ulcer.

Clinicians should be aware that asymptomatic primary hyperparathyroidism can occur and should institute appropriate studies whenever a clue compatible with this disease is encountered. An important corollary to be drawn from this study is that the diagnosis of primary hyperparathyroidism depends exclusively on the accurate clinical interpretation of reliable laboratory data and on pathologic findings; it is not dependent on any combination of clinical signs or symptoms.

Summary. Classically, primary hyperparathyroidism is manifested by symptomatic complications involving the skeleton or urinary tract. However, hyperparathyroidism may cause atypical symptoms or be present even without symptoms. In such instances, the diagnosis may be made by serendipity —the fortuitous discovery of valuable things. We have reported 20 such cases wherein the diagnosis of hyperparathyroidism was unexpectedly made during the investigation of unrelated conditions. In each instance the patient had an elevated concentration of serum calcium which reverted to normal after the removal of a parathyroid tumor. In 4 cases a parathyroid tumor was found during an unrelated surgical procedure. In 9 cases an elevated concentration of serum calcium was found, although the determination had been done originally to rule out the presence of hypocalcemia. In 7 cases nephrocalcinosis, renal calculi, or generalized demineralization of the bones was incidentally noted in roentgenograms taken for unrelated conditions.

These cases are presented to emphasize the fact that hyperparathyroidism may be asymptomatic. The clinician must be aware of this fact and must institute appropriate studies whenever he finds a clue that suggests the presence of hyperparathyroidism.

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SUMMARIO IN INTERLINGUA

Serendipitate In Le Diagnose De Hyperparathyroidismo

Hyperparathyroidismo primari se manifesta in su forma classic per complicationes symptomatic que affice le skeleto o le vias urinari. Tamen, hyperparathyroidismo pote causar symptomas atypic e mesmo esser presente sin ulle symptoma del toto. In tal casos le diagnose depende a vices del "genio del discoperta inexpectate" in le diagnostico, *i.e.* del talento possedite per le tres princes de Serendip in le conto de fees de iste titulo e designate per consequente per le termino serendipitate.

Nos ha reportate 20 tal casos, in que le diagnose de hyperparathyroidismo esseva facite inexpectatemente in le curso del investigation de un completemente differente condition. In omne caso de iste serie, elevate concentrationes del calcium seral esseva notate, e isto reverteva a nivellos normal post le ablation de un tumor parathyroide. In 4 casos, un tumor parathyroide esseva trovate durante un non-relationate intervention chirurgic. In 9 casos un elevate concentration del calcium seral esseva trovate, ben que le determination habeva essite effectuate originalmente pro excluder le presentia de hypocalcemia. In 7 casos, nephrocalcinosis, calculos renal, o dismineralisation generalisate del ossos esseva notate incidentalmente in roentgenogrammas facite pro conditiones non relationate.

Iste casos es presentate pro sublinear le facto que hyperparathyroidismo pote esser asymptomatic. Le clinico debe esser conscie de iste facto. Ille debe instituer le appropriate studios quandocunque ille trova un indicio que suggere le presentia possibile de hyperparathyroidismo.

SEROLOGICAL, ELECTROPHORETIC AND HISTOLOGICAL OBSERVATIONS IN MITRAL COMMISSUROTOMY PATIENTS

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While there is abundant evidence implicating the Group A, beta-hemolytic streptococci as etiologic agents in rheumatic fever (Harris and Harris[5], Harris and Friedman[6]), the exact pathogenesis remains obscure. Detailed observations of patients have suggested that tissue activity may continue in the absence of recognizable clinical signs and symptoms (Tedeschi, Wagner and Pani[17], Tedeschi and Wagner[18]). In an attempt to detect this subclinical state, a variety of laboratory procedures have been proposed (Wood, Bates and McCarty[23]). These procedures may be classified as measurements of acute phase reactants (Stollerman *et al.*[15]) including electropherograms and antistreptococcal antibodies. While no single test can be regarded as specific for the diagnosis of rheumatic fever, the application of a broad group of tests may reflect rheumatic activity. Such data are of importance in establishing a rational therapeutic approach.

The hallmark of tissue activity in rheumatic fever is the Aschoff body (Tedeschi, Wagner and Pani[17]). However, the relationship of this structure to the accepted criteria for clinical activity has been questioned (Manchester *et al.*[10], Tedeschi and Wagner[18]). With the advent of mitral commissurotomy for rheumatic mitral valvular disease, tissue obtained *intra vitam* has been studied. The purpose of this paper is to present a series of correlated tissue, serological and electrophoretic observations in surgically treated rheumatic patients in an effort to delineate the subclinical state of rheumatic carditis.

Materials and Methods. A total of 98 cases operated on for mitral valvular disease was studied. Forty-seven patients were obtained from the Bailey Thoracic Clinic, Hahnemann Medical College, and Drs. R. Glover, R. P. Custer and their associates, Presbyterian Hospital, supplied an additional 51 cases. The patients were regarded as "in-

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active, chronic rheumatic mitral valvular disease" according to well established clinical criteria (Jones[8]). Blood samples were obtained 24 to 96 hours preoperatively in every case and postoperative samples were taken in selected cases. Sera were quickly frozen and stored at −20° C. Biopsies of the left auricular appendage were placed in moistened, sterile gauze and immediately refrigerated. These tissues were divided in half, fixed in cold, neutral formalin and then embedded. Each biopsy yielded an average of 4 tissue blocks which were then serially sectioned at 5μ. Routine stains included hematoxylin and eosin, toluidine blue, elastica van Gieson and PAS.

Erythrocyte sedimentation rates (E.S.R.) were determined by the method of Wintrobe with appropriate corrections. C-reactive protein was measured by the method of Anderson and McCarty[1]. Antistreptolysin O and antihyaluronidase determinations were carried out by Dr. T. N. Harris according to methods established in his laboratory[5]. Filter paper electrophoresis was performed essentially as described by Block, Durrum and Zweig[2] using the Durrum-type cell. Electrophoretic runs (Spinco model R) were made at 40° C. for 24 hours on Whatman 3 MM filter paper strips saturated with 0.075 M barbital buffer (pH 8.6) using a constant current of 5 milliamperes for each cell of 8 strips. All samples were run in duplicate and stained by Spinco dye B–1. A recording densitometer (Analytrol, Spinco) was used to plot the protein concentrations. Chemical determination of serum albumin and globulin was also carried out by routine methods.

Results. E.S.R. were variable and showed no constant relation to the serological response and tissue changes. In the present series, only one case showed a significantly elevated E.S.R. and Aschoff bodies in the subendocardium. A previous study had indicated that the E.S.R. might be the best single test that correlated with the pathological classification of the appendage biopsies (Tedeschi, Wagner and Pani[17]).

C-reactive protein was considered positive in 27 serum samples. Of these cases, 4 showed Aschoff bodies in the surgical biopsy. However, these same 4 cases showed no significant values for antistreptolysin O and antihyaluronidase. In one of these, there was an elevation of beta and gamma globulin to top normal values.

Electropherograms of paired sera samples from 47 patients were analyzed. In 23 patients the alpha-2 globulin was considered to be elevated above the normal range. Ten of these cases and 4 others showed elevated gamma globulin levels. Again, no apparent relationship was noted between the globulin alterations and the other tests performed. The chemical determinations of serum albumin and globulin in 51 patients revealed no gross changes in these protein fractions. In 2 cases with Aschoff bodies a globulin fraction was increased and this only in the alpha-2 zone.

Antistreptolysin O values were considered in the "diagnostic" range in 9 patients. Of these cases, one demonstrated the presence of Aschoff bodies. Antihyaluronidase titers were elevated in 2 cases but were associated with normal values for all other tests.

The histological criteria required for the diagnosis of the typical, mature Aschoff body have been presented in detail (Tedeschi, Wagner and Pani[17], Tedeschi and Wagner[18], Wagner[20]). Using these rigid standards, Aschoff lesions were noted in 8 out of 98 cases. In one of these 8 cases, there were the associated findings compatible with the tissue diagnosis of "acute, rheumatic carditis." However, this same case only demonstrated an elevated C-reactive protein level. Appendages without clear evidence of rheumatic stigmata showed varying degrees of endocardial thickening and sclerosis.

Discussion. In a series of 98 patients subjected to mitral commissurotomy for relief of rheumatic valvular disease, 8 showed histological evidence of rheumatic carditis. The diagnosis of rheumatic carditis was based on the demonstration of unequivocal Aschoff

bodies according to the criteria of Gross and Ehrlich and others (Tedeschi, Wagner and Pani[17]). Scattered, large mononuclear cells, sometimes arranged in groups in the subendocardium, were considered as the late manifestations of previous damage. Including this group of 98, since 1954, we have studied an accumulated total of 648 left auricular appendage biopsies, and only 12 cases have adequately fulfilled the microscopic requirements necessary for the diagnosis of "acute, rheumatic carditis." In addition to these 12, mature Aschoff bodies were noted in 82 cases for a total of 94 or 12.9% of the 648 tissues reviewed. The remaining group was classified by descriptive histopathologic terms since pathognomonic tissue changes were lacking.

Table 1 lists the accumulated data obtained from the patients demonstrating histological evidence of rheumatic carditis. It will be noted that there is little correlation between the tissue response and the other tests. In the single case regarded as acute rheumatic carditis by morphological criteria, the C-reactive protein was positive. Case 4, Table 1, showed the largest number of positive findings. However, this patient was clinically inactive including electrocardiographic studies. While it is not the purpose of this report to comment on the clinical aspects of these cases, nevertheless, the patients listed in Table 1 had uneventful postoperative courses.

As noted by Harris, Friedman and Tang[7], the values found for acute phase reactants and antibodies to two hemolytic streptococcal antigens do not necessarily reflect the subclinical rheumatic state. The observations of Kroop, Heffer and Shackman[9] of the electrophoretic patterns in 36 cases of rheumatic fever indicate that an elevated beta globulin fraction strongly suggests activity. However, they also state that a normal electrophoretic pattern may be obtained in the presence of active rheumatic fever. These authors conclude that electrophoresis is of little absolute value in determining rheumatic activity. Wilson and Lubschez[22] have stated that elevation of the gamma globulin component in rheumatic fever is not a function of the rheumatic process.

Detailed antistreptolysin and antihyaluronidase studies by Harris and Harris[5] have clearly shown the varied response in clinically quiescent cases of rheumatic fever. Cloetens, Mascart and DeMey[4] studied a small series of patients before mitral commissurotomy

TABLE 1.—CORRELATED DATA OF PATIENTS WITH HISTOLOGICAL RHEUMATIC CARDITIS

Patient	*ESR*	*CRP*	*Serum Proteins*	*ASO*	*AH*	*Tissue Diagnosis*
1	—	+	—	—	—	acute, rheumatic carditis
2	Inc.	+	alpha — 2 ↑	—	—	rheumatic carditis
3	—	+	alpha — 2 ↑	—	—	rheumatic carditis
4	—	+	beta, gamma glob. ↑	Inc.	—	rheumatic carditis
5	—	—	—	—	—	rheumatic carditis
6	—	—	—	—	—	rheumatic carditis
7	—	—	—	—	—	rheumatic carditis
8	—	—	—	—	—	rheumatic carditis

Key: —, no change; +, positive reaction
ESR, erythrocyte sedimentation rate
CRP, C-reactive protein; ASO, antistreptolysin O; AH, antihyaluronidase

They found the antistreptolysin level paralleled clinical activity. Tissue findings were not reported. Stadtsbaeder[14], however, did not confirm these observations in a similar group of patients. His studies indicated no significant relationship between the antistreptolysin titer and activity in patients undergoing mitral commissurotomy. The apparent discrepancies may be due to many factors which influence the antistreptolysin response (Chamberlain, St. Hill and Cope[3], Stollerman *et al.*[16]). Antihyaluronidase levels for patients with active rheumatic fever have been found to be significantly higher than antistreptolysin titers (Quinn and Liao[12]). However, antihyaluronidase titers are well within the normal range in quiescent cases.

Previous studies have questioned the clinical significance of the Aschoff body *per se* (Tedeschi, Wagner and Pani[17], Wagner and Tedeschi[19], Wagner[20]). This structure has a clearly defined life cycle and may persist for uncertain periods of time before being obliterated by fibrosis. In our opinion, the Aschoff body remains pathognomonic and unique to the rheumatic process. However, the presence of this structure in the absence of other cellular and connective tissue changes characteristic of acute carditis, limits interpretation as regards activity. Some of the important questions to be considered are: (1) Why do the appendage biopsies with acute rheumatic carditis fail to reflect this process serologically, chemically and clinically? (2) Are the Aschoff bodies in the auricular appendage of equal significance to similar lesions in other areas of the heart? and (3) do Aschoff bodies represent a final morphological expression of different pathogenetic origins?

There is no apparent answer to the first question. One assumption would regard the tests used as insensitive while the other hypothesis would hold that the morphological interpretations are invalid. The observations by Manchester, Scotti, Reynolds and Dawson[10] and McNeely, Ellis and Harken[11] indicate that the Aschoff bodies in the appendages correlate with the demonstration of these structures in the ventricles. Some workers have indicated that there may be a myogenic type Aschoff body and a nonmyogenic Aschoff body (Manchester *et al.*[10], McNeely, Ellis and Harken[11]). This would suggest that under certain circumstances cardiac myofibers are involved in the evolution of the Aschoff body. The origin of the Aschoff cell is of fundamental importance but remains obscure (Wagner and Tedeschi[19], Wagner[20]). It would seem that the detection of subclinical rheumatic activity rests largely on the observation of subtle changes in the status of the patient (Skillman *et al.*[13]). At present there are no measurements which can predict the tissue findings. Much more additional information is needed to further clarify these perplexing matters. Newer immunohistochemical techniques may more closely correlate the serological and tissue findings (Wagner, Pani and Shapiro[21]).

Summary. A series of 98 unselected patients clinically classified as chronic, inactive rheumatic valvular disease were studied prior to mitral commissurotomy and shortly thereafter. Left auricular appendage biopsies in 8 cases were compatible with the tissue diagnosis of rheumatic carditis. Erythrocyte sedimentation rate, C-reactive protein, filter paper electropherograms, antistreptolysin and antihyaluronidase determinations showed no constant relationship to the morphological observations. The tissue findings of rheumatic carditis were not reflected in the immediate pre- and postoperative laboratory measurements. The prob-

lem of subclinical rheumatic activity remains ill-defined by current clinical and laboratory data. When present in the biopsy, the mature Aschoff body must be regarded as pathognomonic of rheumatic carditis.

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SUMMARIO IN INTERLINGUA

Observationes Serologic, Electrophoretic, E Histologic In Patientes Con Commissurotomia Mitral

Un serie de 98 non-seligite patientes, ex le classification clinic de chronic morbo valvular rheumatic inactive, esseva studiate ante e brevemente post le effectuation de commissurotomia mitral. In 8 casos, biopsias del appendice sinistro-auricular esseva conforme a un diagnose histologic de carditis rheumatic. Le rapiditate del sedimentation erythrocytic, le concentration de proteina C-reactive, electrophorogrammas a papiro-filtro, e determinationes de antistreptolysina e de antihyaluronidase revelava nulle constante relation con le observationes morphologic. Le constatationes histologic de carditis rheumatic non esseva reflectite in le mesurationes laboratorial immediatemente ante e post le operation. Le problema de subclinic activitate rheumatic remane mal-definite per le currente datos clinic e laboratorial. Le matur corpore de Aschoff, quando presente in le biopsia, debe esser reguardate como pathognomonic pro carditis rheumatic.

A MEANS OF LOWERING ELEVATED BLOOD CHOLESTEROL LEVELS IN PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION

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The possibility of an interrelationship between dietary fat, blood cholesterol, and coronary atherosclerosis is presently commanding attention. It will be recalled that the original impetus of this theory emerged from epidemiologic surveys on populations, civilizations, or social strata where the available statistics seemed to indicate that a relationship did exist between the incidence of coronary disease and the level of dietary fat (Keys[8,9], Keys and White[12]). While this theory has been questioned by some (Yerushalmy and Hilleboe[19]), it has appeared sufficiently promising to motivate several studies of cholesterol (and lipoprotein) levels in patients with histories of myocardial infarction or angina pectoris, compared to normal individuals of similar age in each sex (Gofman *et al.*[5], Keys[8], Lawry *et al.*[14]). The general indications which have emerged from such studies are: 1. serum cholesterol levels provide as dependable an index of disturbed lipid metabolism as do lipoproteins; 2. *average* cholesterol and lipoprotein levels are higher in myocardial infarction patients (as a group) than the corresponding average for similar aged groups in each sex who do not have overt manifestations of atherosclerosis; and 3. individual differences are so great that neither the cholesterol nor lipoprotein level in any *individual* case can be viewed with certainty as a premonitory sign of present or future coronary disease.

Dietary fat has in turn been scrutinized in terms of saturated versus unsaturated fatty acid content. It was demonstrated that the intake of saturated fatty acids can have a definite effect upon blood cholesterol levels (Ahrens *et al.*[1], Beveridge *et al.*[3], Bronte-Stuart *et al.*[4], Kinsell *et al.*[13]). It appears that the unsaturated type of fatty acid (specifically linoleic and probably arachidonic) can produce a fall in blood cholesterol in the presence of lowered total fat intake and lowered proportion of saturated fatty acids. Less definite have been the results obtained when unsaturated fats are merely added to the normal diet without concurrent reduction in both the total fat content and the proportion of saturated fatty acids (Perkins, Wright and Gatje[17], Tobian and Tuna[18]). This is possibly due to the cholesterol-raising effect of a positive caloric balance (Mann *et al.*[16]). Other questions have arisen incidentally, such as that pertaining to the slight superiority for lowering cholesterol levels reportedly exhibited by corn oil over other vegetable oils which have a higher content

of unsaturated fatty acids (Beveridge, Connell and Mayer[2]).

Materials and Methods. The present study concerns the apparent effects of an unsaturated fatty acid formula (safflower oil plus sitosterol plus pyridoxine plus Vitamin E) upon the blood cholesterol levels of patients with known coronary artery disease, whose daily fat intake had been constant for at least 6 months at one of the following levels: a) less than 50 gm. (10 patients hereafter referred to as Group I); b) between 50 and 100 gm. (8 patients, Group II); c) more than 100 gm. (10 patients, Group III). The subjects were 28 white men, all of whom had previously sustained a myocardial infarction. They were all policemen and firemen of the City of Philadelphia, but they had performed sedentary jobs since their infarctions (and during this study). Their ages ranged from 36 to 53 years, averaging 45.0 years. Their cholesterol levels had been consistently higher than accepted normal, whether their daily fat intake had been low (Group I), intermediate (Group II), or high (Group III).

At least 4, and usually 6 or 8 blood cholesterol determinations had been done on each subject during the 6 or more months preliminary observation prior to this study. Baseline cholesterol levels were, therefore, well established.

Cholesterol was determined by the Abell method. The reproducibility of results by this technique had been previously demonstrated and again verified in our laboratory during this study. The determinations were made by the same technician in the same laboratory, using separate equipment, under research conditions. No attempt was made to obtain fasting blood specimens since it has been demonstrated that recent intake of food has no appreciable effect upon blood cholesterol (Keys *et al.*[10]). Blood was usually drawn 2 hours after the last meal.

The approximate level of dietary fat intake was checked carefully (interrogation and calculation) prior to the study and frequently verified during the course of this study. The motivation of this group of young patients was strong, and there was no reason to doubt the responses made to our interrogations.

The increased intake of unsaturated fatty acids was accomplished by the addition to the aforementioned diets of a safflower oil emulsion, whose natural plant sterol content (0.41%) was fortified artificially to the level of 2% (the maximum compatible with solubility and palatability). One tablespoon (15 ml.) provided 300 mg. plant sterols, 1.0 mg. pyridoxine, and 9.8 gm. of saffllower oil which contained 20 mg. Vitamin E. This formula* is referred to hereafter as "S–S–P." (Safflower oil–Sitosterol–Pyridoxine).

The changes in blood cholesterol associated with the intake of this unsaturated fatty acid formula were determined at each of the 3 levels of dietary fat intake during an initial "therapeutic" period of 3 months (during which it was our objective promptly to lower blood cholesterols which had remained high despite the previous dietary measures). Throughout this time, each subject received 4 tablespoons of the emulsion daily (taken *during* each of 3 meals, and in the evening). Cholesterol was determined weekly for the first 4 weeks, then biweekly for 2 weeks, and once at the end of the third month for a total of 7 determinations during this initial 3 month period. Thereafter, a "maintenance" period of an additional 3 months was effected by reduction of the S–S–P formula to 2 tablespoons daily (with breakfast and dinner). No other changes were permitted; the level of dietary fat remained as it had been during the earlier phase, and the general level of activity was unaffected. Blood cholesterol levels were continued on a monthly basis, as previously. The total elapsed period of study was, therefore, 6 months.

Results. Changes seemingly induced in blood cholesterol levels during any regimen must be assessed cautiously because they might merely reflect daily biologic fluctuation plus the error inherent to the laboratory method. In our experience the potential fluctuation due to these combined factors does not exceed ±40 mg. under the conditions that obtained in this study. We have accordingly considered that any change in blood cholesterol must exceed 40 mg. in order to be considered significant.

"THERAPEUTIC" PERIOD (3 MONTHS). Every subject showed a "numerical" decrease in blood cholesterol at the end of the 3 month period. Drops of significant magnitude (at least 40 mg.

*Provided by Abbott Laboratories.

per 100 ml.) were found as follows: Group III (over 100 gm. fat) 5 of 10 patients (Table 1); Group II (50 to 100 gm. fat), 6 of 8 patients (Table 2); Group III (over 100 gm. fat, 5 of 10 patients (Table 3). (All 3 groups received 4 tablespoons S–S–P daily.)

"MAINTENANCE" PERIOD (SUBSEQUENT 3 MONTHS). *Group I* (less than 50 gm. dietary fat, plus 2 tablespoons S–S–P daily).

In 8 out of 10 cases the level of cholesterol after 3 months maintenance therapy remained within the same range found after the initial 3 month therapeutic period. (Two of these 8 subjects showed additional significant drops despite the reduced dosage.) Two subjects showed an increase greater than 40 mg. during this maintenance period. At the end of the 6 months, all patients in this group had levels significantly lower than originally. This represented a 26% reduction in the group average baseline cholesterol level. Weight changes (6 months) were generally small. Six subjects lost weight, 3 gained weight (up to 4 pounds) and one maintained his original weight (See Table 1).

Group II (50 to 100 gm. dietary fat plus 2 tablespoons S–S–P daily).

In all 8 cases, the level of cholesterol after 3 months maintenance therapy remained within the same range found after the initial 3 month therapeutic period. (One patient showed a further significant drop.) Over the entire 6 months, the final levels were significantly lower than the original baseline in 7 out of 8 cases; this represented a 20% reduction in the group average baseline cholesterol level. Weight changes were greater in this group than in Group I, as expected from the higher caloric intake. Six out of the 8 patients showed a slight weight increase that ranged from 2 to 6 lbs. (See Table 2).

Group III (100 to 150 gm. dietary fat plus 2 tablespoons S–S–P daily). In 10 cases, the level of cholesterol after 3 months maintenance therapy remained

TABLE 1.—CHANGES IN BLOOD CHOLESTEROL AND BODY WEIGHT IN 10 PATIENTS (GROUP I) WHO INGESTED LESS THAN 50 GM. DIETARY FAT DAILY, PLUS S–S–P FORMULA

		Blood Cholesterol (mg./100 ml.)			*Weight in Pounds*		*Height in inches*
Number	*Age*	*Baseline‡*	*After 3 mo.**	*After 6th mo.†*	*Original*	*Net change 6 mo.*	
1.	41	367	278	319	179	0	71
2.	40	288	212	218	180	−3.5	70
3.	47	270	164	198	174	−7	69½
4.	42	289	258	214	200	−4	70½
5.	48	408	367	305	160.5	−0.5	68
6.	49	301	192	185	136	+1.5	67½
7.	44	304	222	240	165	−2.0	69
8.	45	314	252	260	194	+2.0	70
9.	36	403	289	332	160	−1.0	67
10.	37	283	247	230	165	+4.0	68
Group Aver.	42.9	323	248	250	171.8	−1	69

*S–S–P 4 tablespoons daily up to end of 3rd month.
†S–S–P 2 tablespoons daily from 3rd to 6th month.
‡Lowest value obtained.

in the same range found after the initial 3 month therapeutic period. (One subject showed an additional decrease.) Over the entire 6 months the final levels were significantly lower than originally in 7 out of 10 cases. This represented an 18% reduction in the group average baseline cholesterol level. Weight changes were quite definite in this group, all but 1 patient showing increases that ranged from 1 to 13 lbs. (See Table 3).

STATISTICAL ANALYSIS. Statistical analysis of individual blood cholesterol levels for each patient showed them to be stable during the 6 month study

TABLE 2.—CHANGES IN BLOOD CHOLESTEROL AND BODY WEIGHT IN 8 PATIENTS (GROUP II) WHO INGESTED 50 TO 100 GM. FAT DAILY, PLUS S–S–P FORMULA

		Blood Cholesterol (mg./100 ml.)			*Weight in Pounds*		*Height in inches*
Number	*Age*	*Baseline‡*	*After 3 mo.°*	*After 6th mo.†*	*Original*	*Net change 6 mo.*	
1.	43	287	206	174	201	−8	70½
2.	47	273	227	225	173	+6	71
3.	42	302	214	227	185	−4	71
4.	44	301	260	212	246	+6	71
5.	42	293	232	212	181	+2.5	70
6.	45	328	268	262	190	+4.5	70½
7.	46	290	268	254	174	+2	68½
8.	46	304	276	260	184	+2	69
Group Aver.	44.4	297	244	228	186.8	+1.1	70

°S–S–P 4 tablespoons daily up to end of 3rd month.
†S–S–P 2 tablespoons daily from 3rd to 6th month.
‡Lowest value obtained.

TABLE 3.—CHANGES IN BLOOD CHOLESTEROL AND BODY WEIGHT IN 10 PATIENTS (GROUP III) WHO INGESTED 100 TO 150 GM. DIETARY FAT DAILY, PLUS S–S–P– FORMULA

		Blood Cholesterol (mg./100 ml.)			*Weight in Pounds*		*Height in inches*
Number	*Age*	*Baseline‡*	*After 3 mo.°*	*After 6th mo.†*	*Original*	*Net change 6 mo.*	
1.	47	294	230	240	169	+13	68½
2.	46	312	258	208	251	− 6	73
3.	52	293	211	235	156	+ 7	70
4.	53	290	269	242	152.5	+ 4.5	70½
5.	49	322	305	292	199	+ 8.5	71
6.	49	270	192	209	209	+ 1	70
7.	45	306	272	232	182	+12	70½
8.	44	302	260	260	192	+ 7	71½
9.	48	324	293	292	171	+ 8.5	69½
10.	43	310	276	272	184	+ 7	70
Group Aver.	47.8	302	257	248	186.5	+ 6.3	70

°S–S–P 4 tablespoons daily up to end of 3rd month.
†S–S–P 2 tablespoons daily from 3rd to 6th month.
‡Lowest value obtained.

period. With only 2 exceptions, the monthly variations for each patient are within the limits of variability expected from biologic and analytical fluctuations (that is, ± 40 mg. per 100 ml.). The 2 exceptions actually showed a progressive decrease in blood cholesterol during the last 3 months.

In summary, the reduction in blood cholesterol is highly significant ($P < 0.01$) for all patients except patient 5 in Group III. The group decreases in blood cholesterol are shown by the monthly averages for each Group:

		Monthly Average Cholesterol							
Group	*Average Baseline*	*3*	*4*	*5*	*6*	*7*	*8*	*Average of 3 to 8 Months°*	*Average Decrease Below Baseline*
I	323	248	258	260	250	246	243	251	72 ± 6
II	297	244	247	248	228	231	228	238	59 ± 7
III	302	257	258	263	248	256	240	253	49 ± 6

°Ultimately values were obtained for 8 months, that is, 2 months beyond the end of the study herein reported.

GENERAL OBSERVATIONS. 1. After 6 months, all subjects in Group I showed significant decreases in cholesterol as compared to 88% and 70% in Groups II and III respectively. The magnitude of decrease in group average blood cholesterol was greatest in Group I, but similar for Groups II and III despite the appreciable gain in weight by the latter. Individually, the greatest drops in blood cholesterol were attained by certain patients in Group I.

2. Further scrutiny of the individual data indicates that gain in weight is not necessarily incompatible with lowered blood cholesterol levels in certain cases. Thus, significant decreases for the 6 month period were found despite a 4 lb. gain by a patient in Group I; 4½, 6, and 6 lbs. by 3 patients in Group II; and 12 and 13 lbs. by 2 patients in Group III.

3. Ten of the 28 subjects showed evidence of xanthelasma at the start of the study. After 6 months the lesions showed perceptible decreases in size in 3 of these patients whose cholesterol levels had decreased significantly.

4. Three of the subjects had significant angina prior to therapy. Although each of these patients described improvement during this study, and although the cholesterol levels of each did decline significantly, an evaluation of this therapy for coronary insufficiency could not be definitely ascertained.

5. The formula was well accepted and tolerated by these patients. There was, of course, great appeal to the idea of a possible prophylactic approach against further coronary episodes. It is to be remembered that these patients had already sustained infarctions and their motivation to remain on their diets and accept the formula was great.

6. Taking the formula *during* the meal appeared to have some anorectic potential and may have been helpful in limiting the gain in weight shown by Groups I and II.

Discussion. In our opinion, the circumstances of this study represent a practicable compromise between ideal research conditions which require incarceration and strict metabolic control of the subjects, versus the patient-physician teamwork that is attainable in many medical practices. While some criticism can be leveled at the "outpatient" aspects of this study, it does

appear that a true lowering of blood cholesterol was attained in these patients who had the necessary motivation to adhere to a strict experimental regimen.

Although an unequivocal relationship between diet, blood cholesterol and coronary atherosclerosis remains to be demonstrated, there appears to be sufficient suggestive evidence to support the belief that elevated blood cholesterol levels are undesirable and should be reduced in patients who have experienced a myocardial infarction, or who have diabetes mellitus. The most effective means of accomplishing such reduction is uncertain. Our experience during this study would indicate that the use of safflower oil (in combination with sitosterol, pyridoxine and Vitamin E) will effectively reduce elevated cholesterol levels in patients with known hypercholesterolemia and presumptive atherosclerosis. It would appear that blood cholesterol can be lowered more effectively when the dietary fat intake is less than 100 gm. daily.

There have been articles questioning the value of unsaturated fatty acids for reducing blood cholesterol. Most of these studies have been concerned with normal young subjects (for example, medical students and nurses). It is doubtful that a valid comparison can be made with the results in patients with atherosclerosis or hypercholesterolemia, or both. There are indications from studies with radioactive triolein that lipid metabolism in atherosclerosis differs greatly from the normal.

The effectiveness of the combination of a low fat diet and the added unsaturated fatty acid formula appears to be definite in Groups I and II, and highly suggestive in Group III. The fact that half of the subjects on a free choice diet (Group III) showed significant reduction in blood cholesterol suggests that this formula exerted a corrective effect upon the body's mechanisms for controlling blood cholesterol levels. It should be recalled that all of the subjects in this study had been on their respective diets for at least 6 months (in most cases one year) before the addition of this formula, and that the maximum effect attributable to dietary influences alone had presumably been reached long before the current study.

The weight gain that would be anticipated from the added caloric value of the emulsion (about 350 calories daily from 4 tablespoonfuls) appeared mostly in Group III where there was an average increase of 6.3 pounds in 6 months. Despite this gain in weight, no increase in cholesterol value occurred in any subject. Whether this weight gain accounted for the lesser cholesterol-lowering response in this group is of speculative interest.*

Finally, there are obviously many long range questions which remain to be explored. For example, what happens to the excess cholesterol when the blood levels are reduced; is the rate of excretion or metabolism greater, or might the cholesterol be simply redistributed? Recent reports (Gordon *et al.*[6,7], Lewis[15]) strongly suggest increased conversion of blood cholesterol to cholic acid which can be demonstrated in the bile. Again, is ultimate survival benefited by reduction of elevated cholesterol levels, as has been shown to be the case in long term lowering of elevated blood sugar levels

*Throughout this study the dietary fat intake of each patient remained unchanged. However, carbohydrate calories varied in some patients who were aware of the undesirability of gaining weight. Consequently, total caloric levels ranged in Group I from 1100 to 2500; in Group II, from 1500 to 3100; in Group III, from 2300 to 3800.

in the diabetic? Finally, is there a deficiency of unsaturated fatty acids in the American diet, and is this an absolute deficiency, or instead, a relative deficiency in terms of the amounts of the saturated fatty acid content?

Summary. The blood cholesterol levels of 28 hypercholesterolemic myocardial infarction patients have been followed for 6 months during which an unsaturated fatty acid-sitosterol-pyridoxine-Vitamin E formula was added to their pre-existing diets. The 28 patients were grouped according to their previously standardized dietary fat intakes, namely Group I consisted of 10 patients who received less than 50 gm. fat daily; Group II, made up of 8 patients who ingested 50 to 100 gm. fat daily; and Group III, 10 patients who took 100 to 150 gm. fat daily. The baseline cholesterol of each patient had been well established by frequent analyses during a preliminary observation period of 6 to 12 months; in all cases thus had remained persistently elevated; the value used was the lowest attained.

Every subject showed a decrease in baseline blood cholesterol at the end of a 3 month "treatment" period of 4 tablespoonfuls of formula daily with meals. The decrease was maintained (or additionally lowered) during a subsequent 3 month "maintenance" period of 2 tablespoonfuls of formula daily with meals. The over-all change at the end of 6 months was significant for all patients in Group I, and for 7 of 8 and 7 of 10 patients in Group II and Group III respectively. The magnitude of decrease appeared to be influenced by the amount of weight gain, but in no case was there an elevation over the original baseline level, even in the presence of a considerable gain in weight. However, the greatest blood cholesterol decline was found at low and intermediate dietary fat intakes, where weight gain was slight or absent.

ACKNOWLEDGMENTS: We are indebted to Mrs. Portia Birons who ably performed all the laboratory procedures in this study and to Miss Elsie Murphy and Miss Anne Brennan for other technical help. We also wish to acknowledge the careful statistical analyses of data carried out by Mr. Paul Sanders.

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SUMMARIO IN INTERLINGUA

Un Medio Pro Le Reduction De Elevate Nivellos De Cholesterol Sanguinee In Patientes Con Un Historia De Infarcimento Myocardial

Le nivellos de cholesterol del sanguine de 28 patientes hypercholesterolemic con infarcimento myocardial esseva tenite sub observation a transverso 6 menses durante qual periodo un mixtura dietari continente non-saturate acido grasse, sitosterol, pyridoxina, e vitamina E esseva addite al previe alimentation. Le 28 patientes esseva gruppate secundo le previemente establite standards de ingestion dietari de grassia. Gruppo I consisteva de 10 patientes recipiente minus que 50 g de grassia per die. Gruppo II consisteva de 8 patientes recipiente inter 50 e 100 g de grassia per die. Gruppo III consisteva de 10 patientes recipiente inter 100 e 150 g de grassia per die. Le nivello de base del cholesterol in le sanguine del varie patientes habeva essite clarmente establite per frequente analyses durante un periodo preliminari de observation que habeva durate inter 6 e 12 menses. In omne le casos, iste nivello de base del cholesterol habeva remanite persistentemente elevate. Le plus basse valor registrate durante le observation preliminari esseva usate como valor de base.

Omne le subjectos monstrava un reduction del cholesterol del sanguine a infra le valor de base post 3 menses de "tractamento" con 4 coclearatas de suppa del mixtura per die, ingerite insimul con le repastos regular. Le reduction esseva mantenite (o accentuate additionalmente) durante un periodo subsequente de 3 menses de "mantenentia" con 2 coclearatas de suppa del mixtura per die ingerite con le repastos regular. Le alteration total al fin del 6 menses esseva significative pro omne le patientes in Gruppo I, pro 7 del 8 patients in Gruppo II, e pro 7 del 10 patientes in Gruppo III. Le magnitude del reduction pareva esser influentiate per le concomitante augmento del peso corporee, sed nulle caso monstrava un augmento del cholesterol a supra le nivello original de base, non mesmo in le presentia de un considerabile ganio de peso corporee. Tamen, le plus pronunciate reduction del nivello de cholesterol in le sanguine esseva constatate in casos de basse o intermediari amontas de grassia ingerite, que esseva etiam le casos in que le ganio de peso esseva leve o absente.

THE TREATMENT OF RESPIRATORY ACIDOSIS WITH A POTENT CARBONIC ANHYDRASE INHIBITOR (DICHLORPHENAMIDE)

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Carbonic anhydrase is an enzyme which is abundant in renal tubular cells and which, by accelerating the reaction of $H_2O + CO_2 \rightleftarrows H_2CO_3$, plays a vital role in the conservation of bicarbonate and in the maintenance of normal blood pH. Figure 1 shows graphically that the H^+ made available by carbonic anhydrase replaces Na^+ in the $NaHCO_3$ filtered at the glomerulus, so that $NaHCO_3$ is reabsorbed by the tubules. The H_2CO_3 that is formed in the tubular urine gives up its CO_2 which diffuses back into the tubule cells, leaving H_2O to be excreted. H^+ also is available for the conversion of dibasic to monobasic phosphate with conservation of $NaHCO_3$, and enters into the formation of ammonium salts again permitting reabsorption of $NaHCO_3$.

As would be expected, inhibition of carbonic anhydrase results in an increased bicarbonate and sodium excretion, diminished urinary ammonium and titratable acidity, and decreased plasma CO_2 combining power and pH. Furthermore, there is increased K^+ excretion since H^+ and K^+ compete for secretion by the renal tubular cells in the conservation of the Na^+, and reduction in available H^+ furthers the loss of K^+.

Blood pH is not determined solely by CO_2 content but by the ratio of $BHCO_3$ ("base-bound" bicarbonate) to H_2CO_3. In the normal individual with alveolar pCO_2 of 40 mm. Hg, the values for $BHCO_3$ and H_2CO_3 are 26 mM. per L. and 1.3 mM. per L., a ratio of 20 to 1. This relationship is shown in Fig. 2. In respiratory acidosis, the increased alveolar pCO_2 results in an increased plasma H_2CO_3, but the blood pH may be only slightly changed since increased carbonic anhydrase activity occasioned by the elevated pCO_2 (Dorman, Sullivan and Pitts[1]) results in further retention of $BHCO_3$ and in maintenance of the 20 to 1 ratio; that is, the blood $BHCO_3$ has increased along with the H_2CO_3. If now the ability of the body to conserve $BHCO_3$ is impaired; for example, by a carbonic anhydrase inhibitor, and there is no accompanying reduction in pCO_2, then the $BHCO_3$ is depleted, the ratio lowered, and the pH reduced.

The proclivity of sulfanilamide to produce an alkaline urine with increased loss of sodium and the development of hyperchloremic acidosis was noted by a number of observers early in the use of this drug (Strauss and Southworth[17], Marshall, Cutting and Emerson[7]). In 1940, sulfonamides

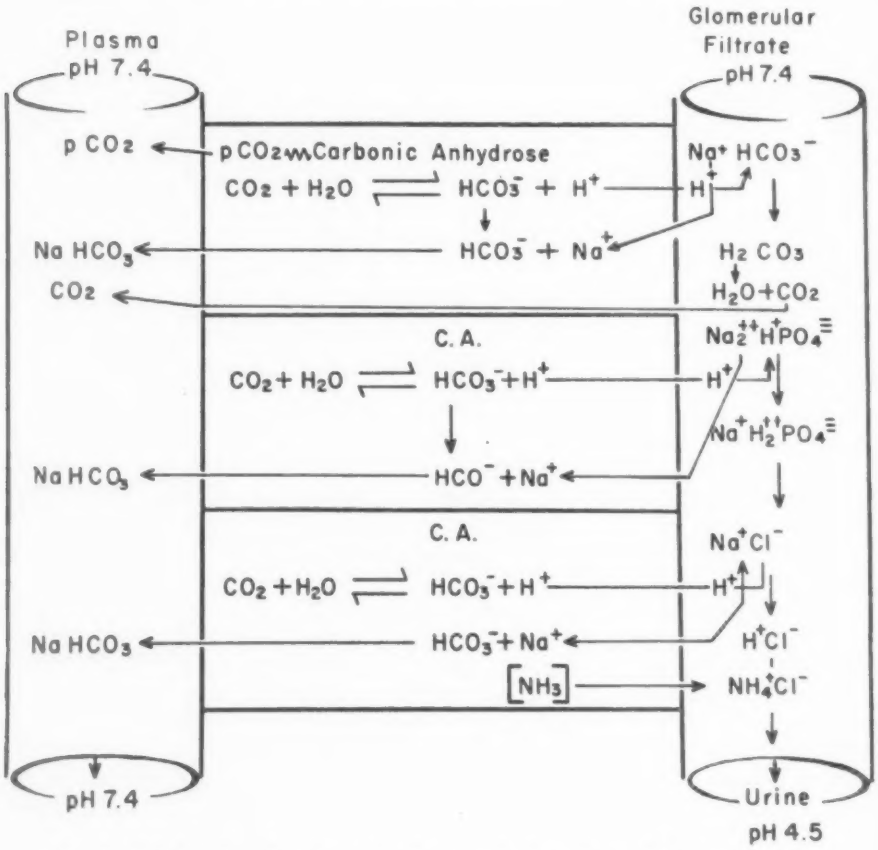

Fig. 1.—Mechanism of action of carbonic anhydrase in acidification of urine.

pH = 6.1 + LOG	$\frac{BHCO_3}{H_2CO_3}$		$\frac{20}{T}$	1.3	= 7.4
"COMPENSATED" RESPIRATORY ACIDOSIS	$\frac{BHCO_3}{H_2CO_3}$ ↑ ↑	<	$\frac{20}{T}$	< 1.3	= < 7.4
"COMPENSATED" METABOLIC ACIDOSIS	$\frac{BHCO_3}{H_2CO_3}$ ↓ ↓	<	$\frac{20}{T}$	< 1.3	= < 7.4
UNCOMPENSATED RESPIRATORY ACIDOSIS	$\frac{BHCO_3}{H_2CO_3}$ ↑ ↑	<	$\frac{20}{T}$	< 1.3	= < 7.4
UNCOMPENSATED METABOLIC ACIDOSIS	$\frac{BHCO_3}{H_2CO_3}$ ↓ ↓	<	$\frac{20}{T}$	< 1.3	= < 7.4
METABOLIC ACIDOSIS PLUS RESPIRATORY ACIDOSIS	$\frac{BHCO_3}{H_2CO_3}$ ↓ ↑	<	$\frac{20}{T}$	< 1.3	= < 7.4

Fig. 2.—Relationship of $BHCO_3$ to H_2CO_3 in acidosis.

were shown to inhibit carbonic anhydrase activity (Mann and Keilin[6]) and later Pitts and his associates, after demonstrating the important role of carbonic anhydrase in maintaining acid base balance, concluded that this mechanism is inhibited by sulfonamide (Pitts and Alexander[11], Pitts *et al.*[12]).

Acetazolamide (Diamox) has been shown to be a potent and nontoxic carbonic inhibitor (Miller, Dessert and Roblin[9]). Reports of its effects on alveolar ventilation in respiratory acidosis disagree regarding the degree, duration, and mechanism of its effects, but in the main noted beneficial results (Nadell[10], Heiskell, Belsky and Klaumann[4], Schwartz, Relman and Leaf[14], Galdston[3]). Fishman, Samet and Cournand[2] concluded, "in any event the demonstration of respiratory acidosis demands the prompt institution of mechanical hyperventilation and Diamox therapy. In addition to its decreasing the alkali reserve Diamox also reduces the arterial pCO_2. The mechanism of this action is not established." Smith noted, however, that the effects of Diamox were self limited apparently by the production of hyperchloremic acidosis which blocks its action presumably by accelerating the activity of the noncarbonic anhydrase-sensitive excretion of H^+ (Smith[16]).

The recent development of another potent carbonic anhydrase inhibitor (Merck[8]), Dichlorphenamide, led us to investigate its effects in patients with chronic lung disease who were under stress to retain $BHCO_3$ because of an elevated pCO_2 and respiratory acidosis.

Dichlorphenamide is a dichlorinated benzenedisulfonamide, which exerts a potent carbonic anhydrase inhibition *in vitro*, and is estimated to be approximately twice as potent as Diamox at its maximal effective dose (Rochelle, Moyer and Ford[13]). It differs from Diamox in causing increased chloride excretion so that it does not produce as marked a metabolic acidosis in large doses, and tends to retain its effectiveness with chronic administration. Like Diamox it may cause anorexia, nausea and vomiting, and certain central nervous symptoms such as nervousness, lassitude, confusion, sedation, dizziness, and so forth.

The purpose of the present study is to determine the effect of dichlorphenamide on arterial blood gases and pH, and renal electrolyte excretion in patients with advanced pulmonary emphysema.

Plan of Study. Eight patients with chronic pulmonary emphysema and pulmonary insufficiency manifested by hypoxia and CO_2 retention were selected for study. Following achievement of maximal benefit from antibiotics, bronchial dilators, and digitalis if cor pulmonale coexisted, they were put on a fixed diet (Na 40 mEq., P 85, C 245, F 95) and given dichlorphenamide*, 50 mg. to 100 mg. twice daily for 10 days. Arterial pCO_2, CO_2 content, pH and O_2 saturation and venous electrolyte studies were done before treatment, on the third and tenth day of the drug, and one week after the drug was stopped. Standard methods for analyses were used. Arterial pCO_2 was calculated from the nomogram of Singer and Hastings[15]. Urinary electrolyte excretion was determined in 4 patients. Urine was collected under oil with 2 drops of phenol as a preservative.

Results. The results are shown graphically in Fig. 3 and in Table 1. It is apparent that, while the arterial pH was significantly reduced initially, it then rose slightly as a result of a continued fall in pCO_2. The total CO_2 content was markedly lowered. These changes began to revert to pre-treatment levels at the time that determinations were made on the seventh day after the drug was stopped. Serum sodium was unchanged, serum potassium tended to fall and serum chlo-

*Supplied as Daranil through the courtesy of Dr. John R. Beem of Merck Sharp and Dohme.

ride to rise. Arterial O_2 saturation rose strikingly.

Table 2 presents the effect of dichlorphenamide on urinary constituents, each value representing the average of daily determinations in 4 subjects. It is evident that there was significant increase in urinary sodium and bicarbonate, and increased excretion of potassium and chloride. The urine pH

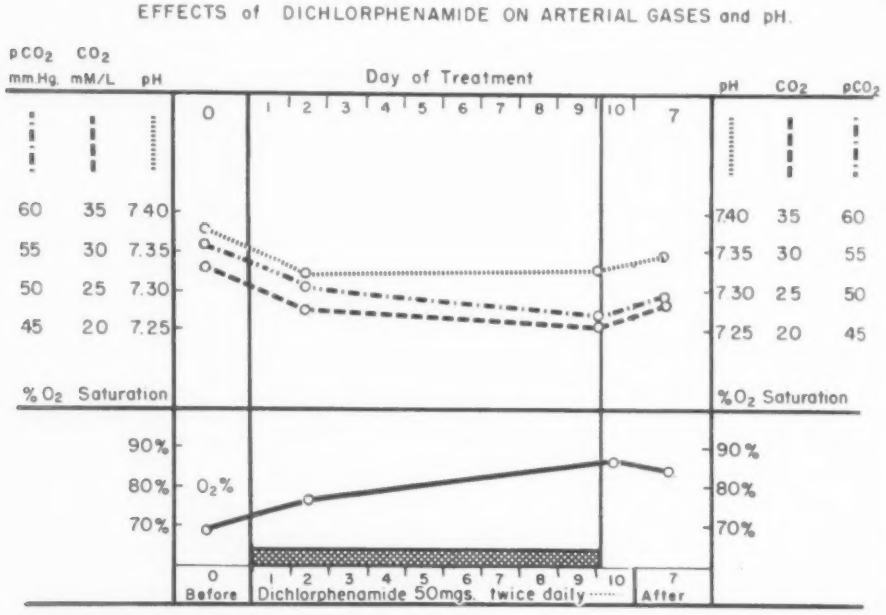

Fig. 3.—Effects of dichlorphenamide on arterial gases and pH: averages of results in 8 patients.

TABLE 1.—EFFECTS OF DICHLORPHENAMIDE ON BLOOD CHEMISTRIES: AVERAGES OF DATA ON 8 PATIENTS

		Dichlorphenamide 100–200 mg./Day		
	Pre-treatment	*36–48 Hours*	*9–10 Days*	*7 Days of Recovery*
	Mean ± 1 s.d.‡	Mean ± 1 s.d.‡	Mean	
Arterial pH	7.381 ± .068	7.320° ± .078	7.325°	7.347
Arterial pCO_2	56.4 ± 10.5	50.2° ± 9.0	46.5°	49.8°
Arterial CO_2 content	27.8 ± 2.35	22.8° ± 2.42	20.6°	23.8°
Arterial O_2 saturation	79.8% ± 13.1	83.2%† ± 13.1	88.4%°	87.3†
Serum Na	138.9	138.9	139.5	138.0
Serum K	5.04	4.50	4.40	4.44
Serum Cl	102.6	107.9°	106.8°	105.6

°—Difference from control mean significant at .01 level.
†—Difference from control mean significant at .05 level.
‡—Mean ± 1 standard deviation.

was alkaline and the volume was increased.

The group as a whole showed sustained weight loss, although the amount could not be correlated with the degree of reduction in arterial pCO_2 or increase in arterial oxygen saturation.

Subjective improvement occurred in each case, and was sometimes marked. Improvement in expiratory wheezes and in pulmonary rales occurred with remarkable regularity in this small group. In 6 of the 8, wheezing completely disappeared; rhonchi were audible on forced expiration only in the other 2. Edema, present in 3 of the patients before dichlorphenamide, disappeared during the treatment period in all 3.

The only side effects encountered were drowsiness and lassitude, which were prominent during the first 2 or 3 days of therapy, improving thereafter.

TABLE 2.—EFFECTS OF DICHLORPHENAMIDE ON URINARY ELECTROLYTE EXCRETION: AVERAGE OF DAILY DETERMINATIONS ON 4 PATIENTS

Day of Treatment	*NA°*	*K°*	*CL°*	*HCO_3°*	*pH*	*Volume*
0	37	35	39.8	1.3	5.5	985
1	129.5	50.8	79.5	29.3	7.2	1237
2	119.7	50.3	125.6	17.8	6.9	996
3	112.3	46.7	98.0	6.5	7.0	1266
4	171.3	44.3	161.3	24.2	7.2	1483
5	141.3	46.7	160.3	6.0	6.8	1243
6	141.5	49.0	181.0	18.0	6.0	1415

°mEq. per 24 hrs.

Discussion. It is evident that with the fall in arterial CO_2 content produced by dichlorphenamide, there is coincident fall in pCO_2 so that the pH, after an initial fall, becomes stabilized. The concomitant increase in O_2 saturation suggests that increased alveolar ventilation accounts for the reduced arterial pCO_2.

The mechanism of the increased alveolar ventilation cannot be explained on present data but may be caused by: 1) Increased ventilatory drive as a result of the initial fall in pH. This is unlikely since, by the seventh day of treatment, pH remained at or slightly higher than on the second day, yet pCO_2 continued to fall and O_2 saturation to rise. 2) Diuresis with drying out of lungs, increase in lung compliance, reduction in secretions and obstruction, and decreased alveolar and interstitial edema with increased diffusion of gases. The weight loss was negligible, however, in several patients who showed a good response. Another patient who had a striking increase in O_2 saturation from 65% to 84% lost 8 pounds after previously having been unresponsive to mercury by injection (Mercuhydrin). 3) A specific effect of dichlorphenamide to reduce bronchial spasm and secretion, and to facilitate alveolo-capillary diffusion of CO_2 and O_2. Further study is underway in an attempt to shed light on this subject. Preliminary studies in 6 young asthmatics have failed to demonstrate consistent improvement in bronchospasm. 4) A recent report (Hilkovitz[5]) that acetazoleamide is beneficial in sickle cell anemia suggests that inhibition of carbonic anhydrase in tissue and red cells prevents the release of O_2 from Hb. and transport of CO_2; that is, the

O_2 stays in the blood and the CO_2 in the tissues. The fact that these patients were clinically improved would hardly be in keeping with the hypothesis that the alterations in blood gases were due to a "tissue poison" effect.

Case Report. One case will be presented briefly as an example of the response to treatment with dichlorphenamide. L.B. is a 67-year-old white man who was hospitalized here in 1950 because of chronic pulmonary emphysema and moderately advanced pulmonary tuberculosis, the latter treated with chemotherapy for 12 months ending May, 1957. The tuberculosis was considered to be inactive for 8 months prior to discharge. Several days before readmission in January, 1958, he developed weakness, anorexia and dyspnea, and was started on tetracycline by his physician. There was progression of his symptoms and he developed a cough productive of yellow sputum that he raised with difficulty.

On admission he was found to be acutely ill, slightly cyanotic, and markedly dyspneic with orthopnea. Breath sounds were distant and rhonchi and wheezes were heard throughout both lung fields. Rectal temperature was 99.2° and remained at about this level throughout his hospitalization. Nonsignificant organisms were cultured from his sputum. His leukocyte count was 10,000, with 78% polymorphonuclears and 22% lymphocytes. The hemoglobin was 13.8 gm., and the hematocrit was 44%. He was given Chloramphenicol, Isuprel, Ephedrine, and oxygen. Although there was some improvement, his dyspnea, cyanosis, and rhonchi persisted. He was started on dichlorphenamide the afternoon of his 5th hospital day and 3 days later it was noted that he was much improved. On the 6th day of treatment his lungs were clear and remained so.

Figure 4 shows the changes in his arterial gases and pH during this period. It is evident that pCO_2 fell in association with HCO_3 so that, instead of developing a deepening acidosis, pH actually rose.

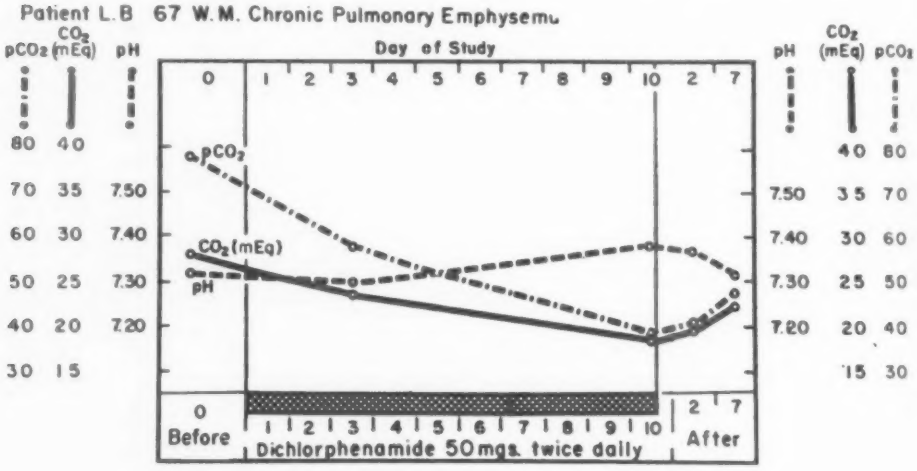

Fig. 4.—Patient L.B., 67 W.M., chronic pulmonary emphysema.

Summary. The effect of dichlorphenamide, a potent carbonic anhydrase inhibitor, in treatment of 8 cases of chronic pulmonary emphysema with respiratory acidosis has been described. During a 10-day treatment period there was decrease in arterial CO_2 content, but concomitant fall in pCO_2, so that the pH was stable or tended to rise after initial depression. Arterial O_2 saturation increased. Serum CO_2 combining power fell and chloride rose; Na and K were essentially unchanged. There was increased excretion of Na,

K, HCO_3, and Cl in the urine. There was significant clinical improvement in every case.

Dichlorphenamide in conjunction with accepted methods of treatment appears to be valuable in the treatment of patients with chronic pulmonary emphysema and respiratory acidosis.

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SUMMARIO IN INTERLINGUA

Le Tractamento De Acidosis Respiratori Per Medio De Un Potente Inhibitor De Anhydrase Carbonic

Es describite le effecto de dichlorphenamido, un potente inhibitor de anhydrase carbonic, in le tractamento de 8 casos de chronic emphysema pulmonar con acidosis respiratori. Durante un periodo de 10 dies de tractamento, occurreva un reduction del contento arterial de CO_2. Etiam occurreva, concomitantemente, un reduction de pCO_2, de maniera que le pH esseva stabile o tendeva a montar post un depression initial. Le saturation arterial de O_2 montava. In le sero le potentia de combinar CO_2 descendeva e le nivello de chloruro montava. Na e K remaneva essentialmente sin alteration. Esseva notate un excretion augmentate de Na, K, HCO_3, e Cl in le urina. Grados significative de melioration clinic esseva notate in omne le casos.

Dichlorphenamido, usate in conjunction con le acceptate methodos therapeutic, pare esser de valor in le tractamento de patientes con chronic emphysema pulmonar e acidosis respiratori.

THE ASSOCIATION OF HYPOGAMMAGLOBULINEMIA AND CHRONIC LYMPHATIC LEUKEMIA

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Brem and Morton[1] in 1955 reported the occurrence of hypogammaglobulinemia in association with chronic lymphatic leukemia in two brothers. Both gave histories of repeated infections such as bronchitis and pneumonia extending over a period of approximately 20 years. Subsequently, both were found to have chronic lymphatic leukemia. Although the serum proteins were determined and the hypoglobulinemia found for the first time after the discovery of the leukemia, the authors believed that the hypogammaglobulinemia preceded the onset of leukemia. Jim and Reinhard[4] reported another case of hypogammaglobulinemia associated with chronic lymphatic leukemia. In their patient the latter diagnosis was established in 1950. Paper electrophoresis done for the first time in 1954 first revealed hypogammaglobulinemia, though it is noteworthy that the patient suffered from 11 episodes of pneumonia between 1950 and 1954.

We have had opportunity to study 6 cases of hypogammaglobulinemia associated with chronic lymphatic leukemia. One (W.S.) also had recurrent basal cell carcinoma and malignant melanoma. The purpose of the present communication is to report these cases and to emphasize that impaired antibody production may be an important factor in the increased susceptibility of such patients to infection and that recognition of this factor may result in better management.

Case Reports. case 1. W.S. (U.H. #923215). This 82-year-old white man was seen at the University Hospital on January 22, 1958, for the first time. One month prior to admission, a swelling under the right mandible and splenomegaly were noted by his private physician. The total leukocyte count at that time was 62,950 per c.mm. with 90% lymphocytes. Past history revealed that during the past 10 years he had recurrent basal cell carcinoma treated on 30 occasions by elective cautery. He also gave a history of pneumonia in 1953 and 1956. Physical examination revealed generalized lymphadenopathy, splenomegaly, presence of a basal cell carcinoma behind his left ear (proved by biopsy), a large 12 × 12 cm. pendulous mass in the right groin (lipoma by biopsy) and a lesion in the right popliteal fossa later shown to be a malignant melanoma by biopsy. Laboratory findings included a hemoglobin value of 12.2 gm.%. The total leukocyte count was 74,000 per c.mm. with 94% mature lymphocytes. Platelets numbered 101,000 per c.mm. Routine urinalysis revealed trace to 1+ proteinuria. Bleeding, clotting and prothrombin times were normal. The total protein value was 6.3 gm.%. Paper electrophoresis revealed the following values: Albumin 4.3 gm.%, $alpha_1$ 0.1 gm.%, $alpha_2$ 0.7 gm.%, beta 0.6 gm.% and gamma globulin 0.6 gm.%. The normal value for gamma globulin in this laboratory (University of Minnesota Hospital Laboratory Services) is 1.1 gm. ± 0.3 gm.%. Bone marrow examination failed to reveal plasma cells. Ninety per cent of the cells were mature lymphocytes. Normoblastic, granulocytic and megakaryocytic hypoplasia were noted. A serologic test for syphilis was negative. No agglutinins were demonstrable for *E. typhosa*, *S. paratyphi B.* or *Brucella*. Heterophile antibodies and cold

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agglutinins were absent. The patient's blood group was O+.

The patient received Roentgen-ray treatment for basal cell carcinoma and underwent excision of the malignant melanoma with radical popliteal node dissection. The patient has failed to return for follow-up. At the time of discharge the leukemia was in fair control and was believed not to need treatment.

CASE 2. V.J. (U.H. #837449). This 65-year-old white man was first seen in the Hematology Clinic in January, 1952, because of generalized lymphadenopathy and splenomegaly. The hemoglobin was 13.2 gm.%, and the total leukocyte count was 56,500 with 97% mature lymphocytes. The patient was followed in the clinic and was believed to be doing fairly well without any treatment. In the summer of 1957 he developed pneumonia and since then has had one recurrence. He was admitted to the hospital in January, 1958, with another attack of pneumonia. Physical examination revealed generalized lymphadenopathy, hepatosplenomegaly and bilateral basilar rales. Chest roentgenogram revealed infiltration in the right lower lung field posteriorly consistent with pneumonia. The hemoglobin value was normal, and the total leukocyte count was 50,000 per c.mm. with 97% lymphocytes. Total serum protein was 5.5 gm.%, with albumin 3.2 gm.% and globulin 2.3 gm.%. Paper electrophoresis revealed albumin 3.2 gm.%, alpha$_1$ 0.2 gm.%, alpha$_2$ 0.9 gm.%, beta 0.6 gm.%, and gamma globulin 0.6 gm.%. Bone marrow was consistent with the diagnosis of chronic lymphatic leukemia. Sputum culture was positive for *Pneumococci*. The patient received Achromycin 250 mg., 4 times a day and improved considerably. Radiologically the lung infiltrate cleared after treatment. Routine urinalysis was unremarkable and serology was negative. After his recovery, serum agglutinins for *E. typhosa, S. paratyphi B* and *Brucella* were sought and none were demonstrable. The zinc turbidity reaction with the patient's serum was 2 units. Blood group was A+ and anti-B titer was nil.

On February 11, 1958, his hemoglobin was 13.2 gm.%, and the leukocytes numbered 32,400 per c.mm. with 98% lymphocytes. The platelet count was 124,000 per c.mm. The patient was advised to return for study and further gamma globulin therapy but failed to do so and on February 26, 1958, suffered another attack of pneumonia at home and expired.

CASE 3. O.N. (U.H.#863430). This 70-year-old white man was found to have chronic lymphatic leukemia in 1953. At that time he had generalized lymphadenopathy and splenomegaly. His hemoglobin was 17.0 gm.%, and the total leukocyte count was 21,250 per c.mm. with 69% lymphocytes. The platelets numbered 121,000 per c.mm. and the reticulocyte count was 2.2%. A serologic test for syphilis was negative. Peripheral blood and bone marrow examination revealed evidence of chronic lymphatic leukemia. The patient has remained asymptomatic, without any treatment. In April, 1958, the physical examination was essentially unchanged. The total protein was 5.9 gm.%, with 4.3 gm.% albumin and 1.6 gm.% globulin. Paper electrophoresis revealed: Albumin 4.4 gm.%, alpha$_1$ 0.3 gm.%, alpha$_2$ 0.5 gm.%, beta 0.5 gm.%, and gamma globulin 0.4 gm.%. The blood group was O+. No serum agglutinins for typhoid and paratyphoid were demonstrable before and after stimulation with repeated triple typhoid vaccine injection. Cold agglutinins and heterophile antibodies were absent. A lymph node biopsy was consistent with chronic lymphatic leukemia or small cell lymphosarcoma. Although this patient has been asymptomatic and has not required treatment, prophylactic gamma globulin therapy was commenced. Currently he is receiving 10 ml. of gamma globulin every 2 weeks.

CASE 4. B.B. (U.H. #894702), a 45-year-old white woman, first noticed enlarged lymph nodes in her neck in 1954. In 1956 a biopsy was performed and showed chronic lymphatic leukemia. Bone marrow examination was also consistent with this diagnosis. There was generalized lymphadenopathy and hepatosplenomegaly. The hemoglobin was 12.9 gm.%, and the total leukocyte count was 123,000 per c.mm. with 91% mature lymphocytes. Platelets numbered 157,000 per c.mm. Paper electrophoresis revealed the following: albumin 4.6 gm.%, alpha$_1$ 0.2 gm.%, alpha$_2$ 0.6 gm.%, beta 0.8 gm.% and gamma globulin 0.5 gm.%. Triple fungi and Mantoux skin tests were negative. The Schick test was positive. Typhoid-paratyphoid agglutinins in serum were absent, both before and after antigenic stimulation. The patient's blood group was O+. The Coombs test was negative. The zinc turbidity reaction with the patient's serum was 1 unit. Chest roentgenogram showed hilar adenopathy. This patient has thus far been asymptomatic. Prophylactic therapy with gamma globulin is being considered but has not yet been commenced.

CASE 5. J.M. (U.H. #926955). This 86-year-old white man was recently referred to

the University Hospital for treatment of basal cell carcinoma. In addition there was splenomegaly. The hemoglobin was 17.9 gm.%, and the white blood cells numbered 19,150 per c.mm. with 18% neutrophils, 80% lymphocytes and 2% monocytes. The platelet count was 96,000 per c.mm., and the reticulocyte count was 0.8%. The bone marrow biopsy findings were consistent with chronic lymphatic leukemia. The serologic test for syphilis was negative. Paper electrophoresis of the patient's serum showed the following values: albumin 4.8 gm.%, alpha$_1$ 0.1, alpha$_2$ 0.4, beta 1.0 and gamma 0.4 gm.%. A chest roentgenogram revealed possibly enlarged mediastinal lymph nodes. The patient received Roentgen-ray treatment for basal cell carcinoma and was requested to return for further observation. However he has failed to return.

CASE 6. J.M. (U.H. #911395), a 60-year-old white man, was admitted to the University Hospital on April 7, 1957. Chronic lymphatic leukemia had been diagnosed 5 years prior to admission, and he had received nitrogen mustard in the interval. On admission he had hoarseness, petechiae, generalized lymphadenopathy, massive hepatosplenomegaly, ankle edema and a few basilar rales bilaterally. The hemoglobin was 8.0 gm.%, leukocytes totalled 476,000 per c.mm. with 100% lymphocytes. The platelets numbered 74,000 per c.mm. The serum iron was 55 mg. per 100 ml. A roentgenographic examination of the chest revealed widening of mediastinum with a number of large lobulated masses in hilar regions as well as behind the left ventricle. Infiltration of the left mid lung field was noted. He received Roentgen-ray therapy to spleen (800r) and neck region (600r) following which the platelets decreased to 45,000 per c.mm. and treatment was discontinued. He was started on Meticorten 5 mg. 4 times a day. In July, 1957, a roentgenographic study of the spine showed compression fractures of first and fourth lumbar vertebrae. In December, 1957, serum protein determination (paper electrophoresis) showed: Total protein 6.2 gm.%, albumin 4.6 gm.%, alpha$_1$ 0.2 gm.%, alpha$_2$ 0.4 gm.%, beta 0.7 gm.%, and gamma globulin 0.2 gm.%. A lymph node biopsy was consistent with a malignant lymphoblastoma. Bone marrow examination revealed thrombocytopenia, megakaryocytopenia, normochromic normocytic anemia, marked lymphocytosis and absence of plasma cells. It was consistent with the diagnosis of chronic lymphatic leukemia. Serum cold agglutinins and heterophile antibodies were absent. The blood group was B negative. Typhoid and paratyphoid agglutinins were absent before and after antigenic stimulation. Skin tests for triple fungi and the Mantoux test were negative. The serum zinc turbidity reaction was 2 units. Routine urinalysis was unremarkable. The blood urea nitrogen was 19 mg. per 100 ml. More recently (January to April, 1958) the hemoglobin has ranged from 11.5 to 12.2 gm.%, the leukocyte count from 45,600 to 279,000 per c.mm. with 97 to 99% lymphocytes and the platelets from 92,000 to 156,000 per c.mm. He is being maintained on Meticorten 15 mg. daily. Prophylactic gamma globulin therapy has been commenced.

Discussion. The association of hypogammaglobulinemia with chronic lymphatic leukemia appears to be rather common. Similar observations have been reported by Wall, Sun and Picklow[9] and Olmer, Mongin and Martin[6]. Wall, Sun and Picklow[9] reported a case in which there was hypogammaglobulinemia at least 2 years before the diagnosis of lymphosarcoma was made. This patient had repeated infections for at least 8 years prior to any manifestations of lymphosarcoma. The report of Brem and Morton[1] also suggests that hypogammaglobulinemia may have preceded the onset of lymphatic leukemia. Study of the present material does not permit any conclusion on this point. The fact that so many cases were observed within a short period of time, definitely indicates a fundamental relationship between the 2 conditions. These cases are different from the syndrome we have previously described[7,8], that of primary acquired hypogammaglobulinemia with splenomegaly and hypersplenism, without evidence of leukemia. In these cases there was only reticular cell hyperplasia, nonmalignant in character. It is recognized, of course, that hypogammaglobulinemia occurs in association with other conditions (Firkin and Blackburn[3]). Lambie, Burrows and Sommers[5] observed it in a case of refractory anemia and thymoma; and we have recently studied a case of re-

fractory anemia without evidence of neoplasm, with hypogammaglobulinemia of 0.6 gm.%, and no antibody titer for *E. typhosa* before or after antigenic stimulation.

Patients with chronic lymphatic leukemia are susceptible to infection and from the present experience, as well as that of others, it is likely that hypogammaglobulinemia is often an important contributing factor. Although paper electrophoresis is a simple and valuable method, the results are only approximate and, of course, give no information as to the quality of the gamma globulin. It is well established that there may be marked increase of an abnormal gamma globulin quite inefficient as antibody, as in multiple myeloma (Zinneman and Hall[10]). Firkin and Blackburn[3] have emphasized the desirability of studying patients with hypogammaglobulinemia as to serum agglutinin titers, and other antibodies, before and after antigenic stimulation. Case 2 in the present series had a gamma globulin concentration of 0.6 gm.% by paper electrophoresis but no evidence of antibody formation and died of recurrent pneumonia. Although some of the patients in the group have had little or no trouble thus far, one can anticipate difficulty sooner or later, and it is believed that such patients should receive gamma globulin at least at the outset of any episode of infection. Whether or not it should be given prophylactically has not been determined, although this appears to be reasonable. Dolowitz *et al.*[2] have reported an increase in the level of gamma globulin following steroid therapy in some patients with hypogammaglobulinemia. They postulate that in such cases antibodies are not adequately revealed normally and that the lymphopenic effect of the steroids liberates a sufficient quantity of antibody to show a rise in the blood level of gamma globulin. Thus there might be a beneficial effect of steroid therapy in patients who have chronic lymphatic leukemia associated with hypogammaglobulinemia, though this has not been proven.

Summary. Hypogammaglobulinemia is frequently associated with chronic lymphatic leukemia. Six cases were observed within a relatively short period. It is suggested that these patients should be studied in this respect since knowledge of hypogammaglobulinemia may improve the general management. One patient with the rare combination of recurrent multiple basal cell carcinoma, malignant melanoma, chronic lymphatic leukemia and hypogammaglobulinemia, is described.

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MULTIPLE KERATOACANTHOMA

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Keratoacanthoma is a benign, ordinarily self-healing tumor of the skin, with histopathologic features indistinguishable from those of invasive squamous cell carcinoma. The tumor has also been described under the terms of multiple self-healing epitheliomata (Dunn and Ferguson-Smith[10], Ferguson-Smith[13,14]), and tumor-like keratoses of Poth[22]. It is by no means an uncommon lesion. In spite of the numerous reports on this tumor in recent years, it is frequently not differentiated from squamous cell carcinoma, with the resultant application of surgical or radiologic therapy which may be unnecessarily drastic and mutilating. On the other hand, there will be instances in which both the clinical and laboratory data are uncertain and indecisive, leaving the physician with no alternative but to proceed with treatment as if the lesion were an invasive and potentially metastasizing carcinoma.

The essential characteristic features of keratoacanthoma are as follows: 1) The lesion arises rapidly over a period of a few weeks, usually on exposed surfaces of the body. A history of recent overexposure to sunlight is frequently obtainable, and the lesions are seen most frequently during the summer months. 2) The characteristic lesion of keratoacanthoma is a papule or nodule in which there is a well-defined central crater containing keratinous tissue. There is a superficial resemblance to the lesion of molluscum contagiosum. 3) Histologically, the tumor shows complete differentiation of the hypertrophic squamous cell elements.

The purpose of this report is to reemphasize this entity, and to report a patient who apparently had been developing lesions of this type for 35 years, and who was recently observed with multiple lesions which were unusually invasive and painful.

Case Report. H.D.S.,* a 56-year-old white boiler maker was first seen by the authors in September, 1957. He gave a history of verrucous growths which had been present on the dorsal aspect of each hand for about 35 years. In 1953, some of these lesions became rather pruritic, and increased in size. Several lesions on the dorsum of the right hand were excised, and a skin graft applied. In 1956 the patient developed a shower of "warts" on his hands, anterior aspect of the chest, and both thighs. These were successfully treated by simple removal, principally by electrocoagulation and curettage. In August, 1956, a lesion on the left hand was treated by electrocoagulation and ionizing radiation therapy. This lesion promptly recurred, was regarded as carcinoma clinically, and was

*Seen through the courtesy of John W. Hurst, M.D., Altoona, Pa.

Fig. 1.—4 October 1957. Verrucous plaque on left wrist. Histopathologic diagnosis: seborrheic keratosis.

Fig. 2.—3 January 1958. Progression to painful raised inflamed tumor, with extension around underlying tendons. Differentiation between keratoacanthoma and squamous cell carcinoma could not be made with certainty. Excision and skin graft done.

widely excised and a split thickness graft applied. The pathologist who examined the specimen felt that it was a verruca with marked epithelial hyperplasia, rather than cancer. Several other recurrences at or near the site of this lesion were removed surgically or treated by ionizing radiation. The pathologic diagnoses on these lesions varied from verrucae to seborrheic keratosis, but none was regarded as cancer.

as being a low-grade epithelioma with features of keratoacanthoma. On the other hand, the surgical pathologist interpreted the same specimen as being squamous cell carcinoma. The patient was referred to the Department of Surgery for further treatment. At that time the lesion was seen as a yellowish, hard, moderately fixed, painful nodule measuring approximately 3 × 1.5 cm. A deep surgical biopsy from the lesion was again diagnosed

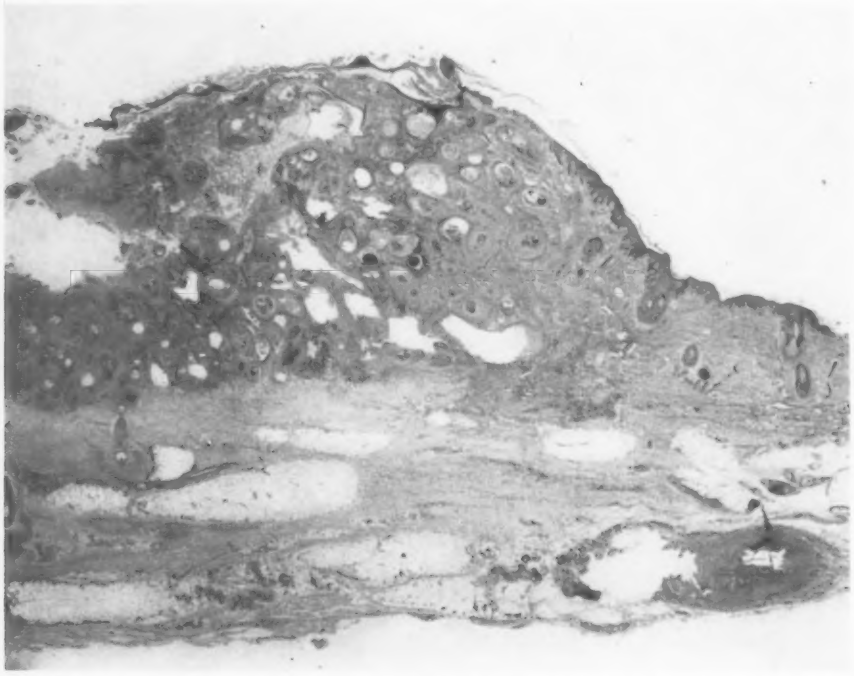

Fig. 3.—Laboratory of Surgical Pathology, Hospital of the University of Pennsylvania #A44879. 10 January 1958. Excision material. Showing various aspects of lesion including the *deep* infection and the prickle cell-like proliferation, actually with configuration of keratoacanthoma.

In September, 1957, a pruritic, nodular lesion with some surrounding erythema, developed on the dorsal aspect of the left wrist. We were asked to see the patient in consultation because of this (Fig. 1). A biopsy from the border of the lesion showed features of seborrheic keratosis. No treatment other than simple local applications to control the pruritus was advised.

The patient was again seen on January 3, 1958, because of a rapid increase in the size of the lesion, and the development of pain and tenderness (Fig. 2). A biopsy from this lesion was interpreted by one of us (H.B.) by the general pathologist as squamous cell carcinoma, but one of us (H.B.) considered it again to be a low-grade epithelioma with features of keratoacanthoma. The advisability of amputation was considered.

On January 10, 1958, Dr. Henry P. Royster of the surgical staff excised the lesion deeply. It had extended to the wrist capsule and around the tendons, and the operative removal was difficult and tedious. There was considerable inflammatory reaction. A skin graft was applied. At the time of operation an enlarged lymph node was removed from the left axilla; this showed no tumor. The

lesion on the wrist was reported by the general pathologist as having been adequately excised, and a histologic diagnosis of squamous cell carcinoma was reported (Fig. 3). The patient was discharged on January 25, 1958.

The patient returned on March 3, 1958, because of multiple recurrences of small tumors in the area of the skin graft, principally on the periphery (Fig. 4). Many of these lesions were typical of keratoacanthoma clinically, pathologic features, correspond to the tumor originally described by Ferguson-Smith as "multiple primary self-healing epithelioma." The prolonged course of the disease, with spontaneous involution of some lesions, and of recurrences, occasionally in the form of a crop of lesions, stamps it as benign, pathologic findings to the contrary. The

Fig. 4.—3 March 1958. Recurrence of typical early lesions of keratoacanthoma in and around lower portion of skin graft.

that is, the nodules had a keratin-filled crater at the summit. The clinical appearance was strongly suggestive of "seeding" of an infection, as is seen in warts. Histologic study of one of the lesions, with serial sectioning, showed the architecture of a low-grade squamous cell carcinoma, with features of keratoacanthoma (Figs. 5, 6, 7). It was concluded that the entire picture, clinical and histopathological, was that of keratoacanthoma. The patient was referred back to his physician, and the removal of individual lesions has since been accomplished satisfactorily by electrocoagulation and curettage.

Discussion. The lesions in this patient, in appearance, course and histo- particular lesion for which we treated the patient was unusually invasive into the subcutaneous tissues and underlying tendons, and very painful.

This type of lesion has received detailed discussion in numerous papers, especially those of Epstein, Biskind and Pollack[11], Ereaux and Schopflocher[12], Binkley and Johnson[4], and Rook and Moffatt[23]. The cause of this peculiar tumor pattern is not known, although there is a strong suggestion that overexposure to sunlight is at least a contributing factor. In our patient, there

Fig. 5

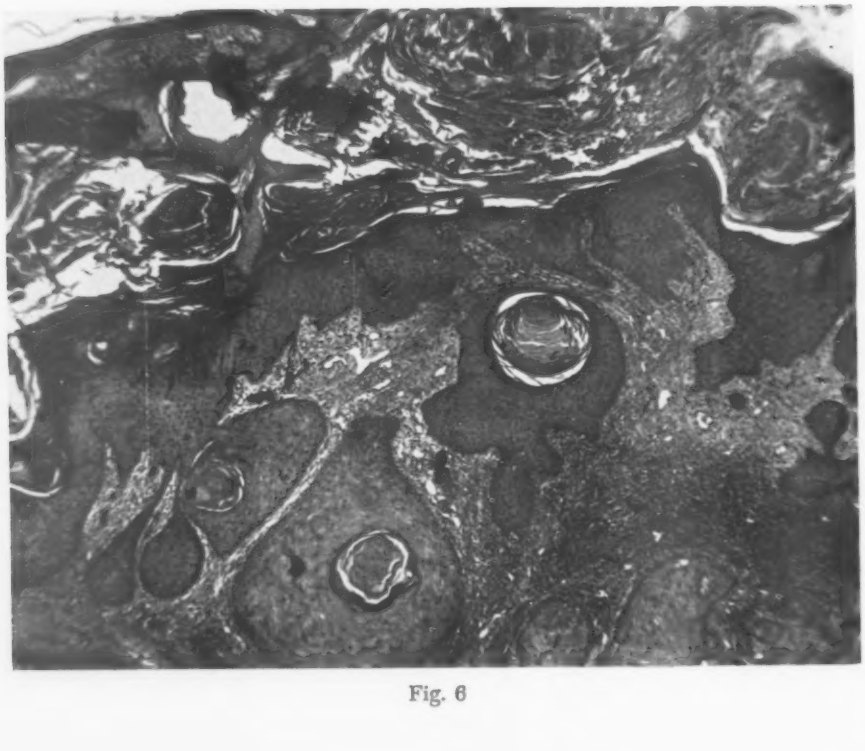

Fig. 6

Fig. 7

Figs. 5, 6, 7.—Department of Dermatology, Hospital of the University of Pennsylvania #H19236.

Lesion removed from donor site. Serial sections (with selections of slides 4, 7, 19).

Note variation in picture from outer edge (seborrheic keratosis-like) to prickle cell epithelioma-like.

This illustrates the value of bisection of the specimen and sectioning the center faces to obtain the characteristic histologic picture of keratoacanthoma.

was a history of unusual occupational exposure to heat, and repeated minor trauma to the hands and forearms. The occurrence of individual lesions, at times in showers, was strongly suggestive of some type of infectious (viral?) disease. There was clear indication in our patient that many of the lesions of keratoacanthoma were preceded by lesions which were indistinguishable from common verrucae or seborrheic keratoses; others, however, arose rapidly on normal skin or scar tissue.

Epstein, Biskind and Pollack[11] summarized the essence of the problem of histologic diagnosis of keratoacanthoma in the following statement: "Histologic examination of a single lesion without knowledge of the clinical picture commonly poses a problem in differential diagnosis. The degree of pseudoepitheliomatous hyperplasia and the modified papillary formation of the epithelium in the depths of the crater often resemble so-called low-grade cornifying epidermoid carcinoma. At these points the changes in epithelial cells are almost impossible to distinguish from true, early invasive carcinoma. However, it is rare to find a degree of pleomorphism and mitotic

activity characteristic of neoplasia. When tissue from several excisions is examined, the uniformity and the basic pattern becomes apparent and distinction between pseudoepitheliomatous hyperplasia and early neoplasia can be made."

That this is not always the case is indicated by the further statement that, although the differentiation from neoplasia is duplicated and confirmed in the lesions of their case, "there is still some zone of proliferating epithelium where, after examination, one is left with the impression that the distinction between pseudoepitheliomatous hyperplasia and neoplasia may not always be clear-cut." Bowman and Pinkus[5] state categorically, on the basis of their own experience and that of others (Fouracres and Whittick[17], Marshall and Findlay[20]), that the "histologic differentiation between keratoacanthoma and so-called self-healing squamous cell epithelioma of the skin, may be difficult if not impossible. Just as difficult is the more important differentiation from true progressive carcinoma. A biopsy specimen of almost all these lesions will appear as a keratinizing epidermoid carcinoma. Histologic Grade I (Broders)."

McNulty and Sommers[21] consider keratoacanthoma to be a surgical pathological entity. They present a detailed differential in Table 2.

It will be noted that their criteria of distinguishing keratoacanthoma and epidermoid carcinoma are based principally on an absence of the more reliable signs of invasion and anaplasia characteristic of true cancer.

The literature is replete with well illustrated descriptions of the so-called characteristic histologic features of various types of keratoacanthoma (Bowman and Pinkus[5], deMoragas, Montgomery and McDonald[9], Dunn and Ferguson-Smith[10], Ereaux, Schopflocher and Fournier[12], Ferguson-Smith[13], Flegel[15], Flielgelman and Loveman[16], Fouracres and Whittick[17], Hamperl and Kalkoff[18], Rook and Whimster[24], Sommerville and Milne[26]). In a study devoted largely to the histopathologic criteria for diagnosis Skirpan and Haserick[25] point out that "the lesion is characterized histopathologically by 1) projection above the plane of the adjoining epidermis; 2) hyperkeratosis of the adjoining epidermis; 3) a central crater with over-lapping edges in some instances; 4) pseudoepitheliomatous hyperplasia marginally and acanthotic squamous-cell-like nests centrally; and 5) a slight-to-moderate chronic inflammatory reaction in the surrounding corium. In addition, the squamous-cell nests contain prominent intracellular bridges, central keratinization, little central necrosis, and a few mitotic figures." They also found that the

TABLE 1.—DIFFERENT POINTS OF KERATOACANTHOMA AND TRUE MALIGNANT SKIN LESIONS*

Keratoacanthoma	*Squamous-Cell Carcinoma*
May resemble molluscum contagiosum	Usually does not resemble molluscum contagiosum
Rapid growth	Generally slower growth
Large keratin plug in crater	A single large plug generally absent
Extremely friable surface	Variable friability
Exocytosis	Lack of exocytosis
Basal-cell layer intact	Basal-cell layer not intact
Overhanging of normal epithelium	Often absence of overhanging epithelium

*From "Keratoacanthoma (Molluscum Sebaceum)." **Bowman, Harold E.**, and **Pinkus, Herman:** A.M.A. Arch. Path., **60**, 19, 1955.

periodic-acid-Schiff stain, the cells of the stratum granulosum and the squamous-cell nests contained prominent, cytoplasmic, periodi-acid-Schiff positive granules. These were lacking in most of the squamous-cell nests in overt carcinomas.† The most significant differential points between keratoacanthoma and squamous-cell carcinoma are:

"(A) The central crater and verruciform appearance.

(B) The superficial resemblance to molluscum contagiosum.

(C) The completely differentiated appearance of the hypertrophic squamous-cell elements."

An important item in the interpretation of the histologic findings is the age of the lesion. As the process approaches spontaneous resolution, there are sloughing of the keratin, atrophy, and appearance of giant cells. Eventual healing may be complete.

Currie and Ferguson-Smith[8] stated that all 10 lesions from a patient and one from his brother showed active squamous-cell epithelioma. They noted "It may be stated categorically that the tumors in the active stage are structurally squamous-cell carcinomata of the skin, which satisfy the accepted histological criteria of malignancy, albeit of low grade. These growths, though active, are well differentiated. Invasion is by infiltrating columns, most of which are continuous with the surface epithelium. Keratinization is prominent. Prickle cells are numerous and palisading of the periphery of the groups of infiltrating cells is often marked. Mitoses are few. Invasion of

TABLE 2.—COMPARISON OF PATHOLOGIC FEATURES OF KERATOACANTHOMA AND EPIDERMOID CARCINOMA*

Gross	*Keratoacanthoma*	*Epidermoid Carcinoma*
Size	Large	Usually small
Shape	Crateriform	Irregular
Color-cut surface	Yellow-tan	Gray
Consistency	Pulpy-moist	Hard-dense
Microscopic		
Adjacent epithelium-basal cells swollen and palisading lost	Characteristic	Uncommon
Epithelial downgrowths	Cohesive, rounded masses	Lack cohesion, pointed
Anaplasia	Absent	Present
Abnormal mitoses	Outnumber normal	Less common
Round red cell degeneration	Characteristic	Absent
Vacuoles	Common, compress nuclei	Absent
Basal cell layer	Absent	Locally absent
Inflammatory infiltrate:		
In epithelium	Marked	Scanty
Around epithelium	Heavy	Irregular
Spindle cell proliferation	Occasional	Infrequent
Fibrillar degeneration of collagen	Characteristic	Infrequent

*From "Keratoacanthoma as a Surgical Pathologic Entity." **McNulty, John R.**, and **Sommers, Sheldon C.**: Surg., Gynec. and Obstet., **104**, 663, 1957.

†In this connection Winer (discussion of Binkley-Johnson's paper) suggests that the uptake of radioactive phosphorus may be of help in differentiation of keratoacanthoma from prickle cell epithelioma.

lymphatic channels is exceptional and has not been previously recorded in this disease. There is a tendency to latent rather than deep infiltration and with few exceptions . . . invasion does not extend much beyond the roots of the hair follicles and sweat glands. These features are not, of course, peculiar to this type lesion; any or all of them may be seen in the familiar single highly-differentiated squamous cell carcinomata."

In the literature (Binkley and Johnson[4], Bowman and Pinkus[5]) a feature considered characteristic of keratoacanthoma is the marginal buttress formation. This results from the fact that invasive epithelium undergrows the normal epidermis and pars papillaris of the surrounding skin, which, in turn, overhangs the central crater. This feature, however, may be found as well in epidermoid carcinomas of varying degrees of malignancy and appears dependent solely on the gross type of growth of the individual lesion. While it is apparently a constant factor in keratoacanthoma, it can be recognized only in favorable sections through the center of the tumor, but not in tangential sections or in small biopsy sections of a large lesion. One fact is certain, and that is a suspected keratoacanthoma never goes beyond the state of Grade I prickle cell carcinoma in appearance, in contrast to the clinical history of rapid development over a few weeks.

Brown and Fryer object to the term "self-healing epidermoid carcinoma" since in no case reported did the patient recover from his disease, only individual lesions recovered. They believe we are left with the situation that 1) if lesions that appear to be carcinomas heal themselves, even though confirmed by pathologists, they probably are not carcinomas and the microscopic findings are not infallible; 2) whether the lesions are carcinomas or not, the tendency continues and apparently becomes worse so that the lesions eventually seem to resemble carcinomas more closely and finally overcome the healing tendency; 3) so far, in no case of self-healing carcinoma reported has the patient been found to be permanently free of the tendency without further evidence of the disease if followed over a period of years. They, too, presented a patient who had multiple growths on 2 split-graft donor sites, which histologically were epidermoid carcinomas. Eighteen lesions healed with no recurrence in 6 years.

Another complicating factor in the histologic diagnosis is that a number of patients with so-called keratoacanthoma have developed true carcinoma (Anderson[1], Beare[2], Belisario and Linn[3], Charteris[7], Zoon, Jansen and von Baak[27]).

From this sampling of the widely prevalent uncertainty in the minds of many pathologists as to the existence of really reliable histopathologic criteria for the diagnosis of keratoacanthoma (multiple self-healing epitheliomata) the dictum of Levy, Cahn, Shaffer and Beerman[19] holds: "It is, therefore, necessary to correlate the clinical with the histopathologic features." Since the clinician must respect the opinion of the histopathologist and is in duty bound, when the diagnosis is made histologically, to do something definitive, decision as to whether the treatment should be conservative or drastic poses a difficult decision.

Summary. 1. A patient is reported who, over a period of many years, had developed lesions of the skin which were variously diagnosed as ordinary verrucae, seborrheic keratoses, and squamous cell carcinomas. In the most recent episode, a lesion on the wrist was observed to progress from a ver-

rucous plaque to a fungating painful tumor which invaded the underlying subcutaneous tissues, and which was surgically excised with considerable difficulty. Following operation, multiple recurrences of lesions typical of keratoacanthoma were noted in and around the skin graft.

2. In a majority of cases, the differentiation of benign keratoacanthoma from malignant squamous cell carcinoma can be made by careful consideration, jointly, of the clinical course of the tumor and its histopathologic characteristics. There remains, however, a residuum of cases in which absolute and positive differentiation is impossible.

3. It is impossible to distinguish keratoacanthoma from Grade I squamous cell carcinoma histopathologically, particularly if only a portion of the lesion is examined. This is a problem of pressing practical significance which deserves increasing attention from experimental pathologists.

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SUMMARIO IN INTERLINGUA

Kerato-Acanthoma Multiple

1. Es reportate le caso de un patiente qui, in le curso de multe annos, habeva disveloppate lesiones cutanee, variemente diagnosticate como verrucas ordinari, keratoses seborrheic, e carcinomas a cellulas squamose. Al occasion del plus

recente episodio, il esseva observate que un lesion al carpo progredeva ab le configuration de un placa verrucose in un tumor dolorose que manifestava fungation, invadeva le subjacente histos subcutanee, e esseva excidite chirurgicamente con considerabile difficultates. Post le operation, multiple recurrentias de lesiones typic de kerato-acanthoma esseva notate in le graffo cutanee e vicin a illo.

2. In le majoritate del casos, le differentiation inter benigne kerato-acanthoma e maligne carcinoma a cellulas squamose pote esser effectuate per le meticulose e simultanee consideration del curso clinic del tumor e de su characteristicas histopathologic. Remane, nonobstante, un residuo de casos in que le absolute e positive differentiation es impossibile.

3. Il es impossibile distinguer kerato-acanthoma ab carcinoma a cellulas squamose de Grado I per medios histopathologic, specialmente si solmente un portion del lesion es examinate. Isto es un problema de urgante signification practic que merita le augmentate attention del pathologos experimental.

SUMMARIO IN INTERLINGUA

(See page 567 for original article)

Post-Dialytic Balancia Acido-Base In Patientes Con Uremia Chronic

Le alterationes del balancia de acido e base durante e post hemodialyse esseva studiate in 5 patientes uremic. Omne le patientes exhibiva initialmente acidosis metabolic con un reducite concentration de base tampon. Isto retornava verso le norma in le curso del dialyse, primarimente a causa de un augmento in le fraction de bicarbonato. Ist immediate alterationes chimic non esseva correlationate con le retardo in le declaration del melioration clinic. Tamen, le 3 patientes qui manteneva lor meliorate stato del balancia acido-base durante un periodo post le dialyse manteneva etiam lor melioration clinic, durante que le 2 patientes qui manifestava un rapide re-apparition de lor acidosis metabolic manifestava etiam un rapide deterioration clinic.

SUMMARIO IN INTERLINGUA

(See page 610 for original article)

Le Association De Hypogammaglobulinemia Con Chronic Leucemia Lymphatic

Hypogammaglobulinemia occurre frequentemente in association con chronic leucemia lymphatic. Sex tal casos esseva observate in le curso de un relativemente breve intervallo de tempore. Es urgite que patientes del genere sub discussion es studiate in iste respecto, proque le cognoscentia de hypogammaglobulinemia pote meliorar le tractamento in general. Es describite un patiente con le combination rar de recurrente carcinoma multiple a cellulas basal, melanoma maligne, chronic leucemia lymphatic, e hypogammaglobulinemia.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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SUBSTANCES USED IN TREATMENT OF DIABETES MELLITUS

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AT present there are two substances available commercially for the treatment of diabetes mellitus. One of these is the insulin group, the other the sulfanylureas. Both are being used extensively here and abroad, and since data in connection with their use are accumulating rapidly as evidenced by the legion of papers appearing in the literature, it was thought that a brief resumé and a critique of them would be timely and helpful. It is the purpose of this review, therefore, to discuss the various insulins now available for the treatment of diabetes, as well as bring up-to-date our knowledge of the practical application of the sulfanylureas.

INSULIN. This is a protein hormone isolated from the beta cells of the pancreas. The mixtures of beef and pork pancreas are the sources from which insulin is prepared. There is also a "special" insulin made from beef pancreas only. The finished product is marketed in 10 ml. vials as U 40 and U 80, that is 40 or 80 units per ml. Higher concentrations can be prepared. Insulin was crystallized by Abel[1], and 1 mg. of the crystals has a potency of 24 units. All insulins contain small quantities of zinc. The active principle lies in the insulin molecule whose speed of action and duration of effect are governed by the addition of a simple protein, a buffer, and the adjustment of the pH. To the physician there are available commercially the following types for therapeutic use:

1) Unmodified Insulin (plain, regular), fast acting.
2) Zinc Insulin Crystals (crystalline insulin), fast acting.

3) Protamine Zinc Insulin, slow acting.
4) NPH Insulin (Isophane), intermediary.
5) Globin Insulin, intermediary.
6) The Lente Insulins:
   a) Semi-Lente, fast acting.
   b) Lente, intermediary.
   c) Ultra-Lente, slow acting.

The plain and crystalline insulins are clear colorless liquids whose pH is 2.5 to 3.5. They contain up to 0.4 mg. of zinc per 100 units and no buffers. Both are rapidly absorbed, show a hypoglycemic effect within one hour, reach their maximum activity at 3 to 4 hours and then their activity decreases though the total duration of effect may last up to 8 hours. These insulins are quite stable at room temperature, but refrigeration is advisable when a large supply is on hand.

Protamine Zinc Insulin, a product introduced by Hagedorn and his associates[10], is a mixture of insulin with 1.0 to 1.5 mg. of protamine, a simple protein, and up to 0.25 mg. of zinc per 100 units. It is also buffered with Na_2HPO_4 and its pH lies between 7.1 and 7.4. It has the appearance of a lactescent liquid which on standing, separates out as a fluffy white precipitate and a clear supernatant fluid. The activity lies in the precipitate and to obtain smooth activity, the particles must be distributed uniformly. This is done by gentle shaking of the bottle. When injected subcutaneously, a supply depot is formed from which the insulin is slowly liberated by the body fluids. The action begins in about 4 hours, reaches a peak in 10 to 24 hours with a residual activity continuing up to the second day. Because of this extremely slow effect, protamine zinc insulin was used with crystalline insulin as a mixture in various proportions, with the hope of obtaining a preparation whose activity would lie between the two extremes. After various trials it was found that a 2:1 mixture of crystalline and protamine zinc insulin produced the most practical and smoothest effect in the majority of patients. In exceptional cases where the physician was dissatisfied with the results he could alter the proportions until diabetic control, according to his standards, was achieved. The action of a Regular (two) and PZI (one) mixture, begins about 2 hours after administration, reaches its peak between 8 to 10 hours and though its activity dwindles its effectiveness may remain for 24 or more hours.

One of the most popular insulins is NPH or isophane insulin. This also has the appearance of a milky liquid. It contains 39 to 55 mg. of protamine and up to 0.4 mg. of zinc per 100 units. It is buffered with Na_2HPO_4 and its pH is 7.1 to 7.4. Its time of action parallels that of 2:1 regular, protamine zinc insulin mixture and its time of effectiveness is best suited for the requirements of the larger group of diabetic patients. It requires no mixing and, therefore, has the advantage of simplicity. Because it too contains the active material in the finely divided precipitate the vial must be agitated gently as with protamine zinc insulin, prior to use.

Globin Insulin is also used widely, and its time of effectiveness is about the same as that of NPH insulin beginning in about 2 hours after injection, reaching a peak between 8 and 12 hours and then its activity dwindles. It is a clear fluid with a pale yellowish tint. It is a mixture of purified globin (from beef hemoglobin) and crystalline insulin. There are 3.8 mg. of globin and 0.30 mg. of zinc to every 100 units. It also contains 1.5% glycerine, no buffer, and its pH is 3.6. After administration the insulin is partially precipitated, from which it is slowly liberated by the

tissue fluids. Thus its action is prolonged.

The Lente Insulins. This is a small group of insulins with a range of activity from that of regular insulin to longer than protamine zinc insulin, depending upon the physical properties of the precipitate produced, amorphous or crystalline. The remarkable major difference between this group and other insulins is that they do not contain a retarding protein. They were developed by Hallas-Møller and his associates[11,12], who found that small quantities of zinc (0.5 to 2 mg. per 1000 units) added to crystalline insulin, resulted in a slowly soluble complex at the blood pH. They also noted that quantities of zinc up to 18 mg. per 1000 units did not retard the action of the suspension more appreciably than the smaller doses of zinc. All of the 3 insulins developed by these investigators contain up to 0.25 mg. of zinc per 100 units and a sodium acetate buffer. In the presence of this buffer, the zinc, and the insulin, two physical forms of insulin zinc suspensions have resulted each with its own time of action. The third is a mixture of the two. Thus there is the semi-lente which is an amorphous precipitate at the blood pH. When a suspension of this is injected it is absorbed readily and has a slightly longer action than regular insulin. With the pH adjusted in the area of 4.8 to 5.7 (Peck *et al.*[18]) crystals of insulin zinc are obtained. They are quite insoluble, and have a prolonged action comparable to protamine zinc insulin. This has been called ultra-lente. A mixture of 70% of ultra-lente and 30% semi-lente yields a preparation which has a curve of activity comparable to NPH and Globin insulin. This is called Lente insulin.

USES OF INSULIN. To treat practically all of the facets of diabetes, the healthy and the sick, one needs only two types of insulin: the fast-acting for all emergencies and the intermediary for the healthy ambulatory diabetic. Regular or crystalline insulin is available for the former, while NPH, Globin or Lente for the latter. In this country NPH and Globin are the every-day insulins for the greatest number of diabetic patients. These two and Lente are practically interchangeable unit for unit. As a matter of routine, however, the physician usually selects one, and more or less, develops the habit of prescribing it.

The emergencies, such as ketosis with acidosis, coma, surgical patients and infections must be treated with the most rapidly acting insulin, namely, crystalline or regular. These types are the only insulins that can be used intravenously. They can be given directly into the vein or they can be introduced into the infusion material whenever the circumstances call for hydration by such means. This does not imply, however, that they should be given by vein in all emergencies. Their effectiveness is excellent when given hypodermically, but as a matter of convenience at times the intravenous route may be desirable.

By contrast, none of the intermediary and slow-acting insulin can be given by vein.

COMPLICATIONS. *Hypoglycemic reaction.* This is the most common complication observed in insulin-treated diabetics. It is caused by insulin overdosage, or insufficient food intake, or physical exercise with the customary dosage, or any combination of these. The patients learn to recognize the symptoms which represent disturbances of the sympathetic nervous system and are characterized by hunger, sweats, tremors, nervousness and headache. They can be relieved rapidly and a bout of unconsciousness aborted by taking some fruit juices at once and

food immediately thereafter. Should the premonitory symptoms go untreated unconsciousness may ensue and require glucose intravenously for recovery.

With the fast-acting insulins, the premonitory symptoms are quite definite and the patient can recognize and treat them. The hypoglycemic phase occurring when the slow acting insulins are used is subtle in onset and the warning signs can be lacking entirely, and even if present they may be so mild that they are overlooked by the patient. To avoid hypoglycemic coma in patients taking slow-acting insulins a glycosuria is desirable at all times. However, if the physician wishes chemical control, the patient should be instructed to take orange juice or other forms of sweets the moment he experiences a feeling of nervousness, headache or *any unusual* and *unexpected abnormal state*. The reactions due to long-acting insulins may be alarming and the patient may remain comatose for hours and even days in spite of a constant infusion of a 5 or 10% glucose solution. Death, though infrequent, does occur. This emphasizes the importance of preventing reactions by treating them at the earliest possible time, at the time they are suspected though not even present. It is wiser and safer to err on the side of a hyperglycemia than that of a hypoglycemia.

Allergy to Insulin. Generalized allergic reactions to insulin are rare. They do occur, however, and may be quite severe, alarming and are characterized by generalized urticaria and its concomitants. This complication rarely occurs in the initial phase of therapy, but develops during its course or after the resumption of insulin after a period of its discontinuance. It is important to desensitize such patients, as a situation may arise where the use of insulin would be lifesaving and the contraindication for its use must be eliminated. As an alternate procedure Dolger[6] suggested destroying the allergic component by immersing the vial of insulin in boiling water for 30 minutes. He cites 4 cases treated successfully by this technique. About 25% of patients treated with insulin show a localized sensitivity. This is characterized by variable sized localized areas of induration, redness, heat, and pruritus at the site of injection. These areas may last for 2 or more days and then disappear. Occasionally, a site of a former reaction flares up, when insulin is given in an entirely different area. As such reactions cease after 2 to 4 weeks of therapy, the patient can be assured of their harmlessness when they occur. Cold compresses usually afford relief both from the heat and pruritus.

Insulin Resistance. When without apparent cause inordinately large amounts of insulin are required to maintain a patient free from symptoms of diabetes and ketonuria, insulin resistance may be considered present. Martin[16] defines insulin resistance as a hyperglycemia lasting over 48 hours and requiring 200 units or more for the lowering of the blood sugar. This is an arbitrary figure accepted by agreement rather than from experimental data. This condition may be temporary and after using hundreds of units for a considerable period of time, one may be able to resume the more conventional doses of 40 to 60 units. Fortunately, for most patients insulin resistance is temporary, but occasionally such a state may not be reversible as noted in one of my patients who required 750 units of insulin daily for 10 years to be free from the symptoms of diabetes and ketonuria, but who revealed a continuous glycosuria. She died at the age of 72 from a cerebrovascular accident and the postmortem studies failed to show any morphologi-

cal aberrations of the pancreas, pituitary and the adrenals.

When insulin resistance develops in a patient, the one and only course to pursue is to give him as much insulin, thousands of units if necessary, to eliminate ketonuria and maintain the urine ketone free. Such prodigious doses must be kept up to tide the patient over from lapsing into ketoacidosis and hoping that a more average insulin unitage may be resumed in this self-limiting condition.

Insulin Lipodystrophies (Barborka[2], Depisch[5]). In some individuals to whom insulin is given, there occur areas of either localized atrophy or hypertrophy of the subcutaneous fat. The former is more common and is noted as depressed areas about 1 cm. in depth and 10 to 20 cm. in diameter. They are painless and free from any inflammatory reactions. These lesions are much more common in women and children and pose a cosmetic problem. It was thought that the repetitive use of a site predisposed to these atrophic or hypertrophic lesions, but the evidence has not been convincing. In one patient the hypertrophies were so marked at the lateral lower third of the thighs to give the effect of "riding breeches." The cause for these complications is unknown and no techniques are known to prevent them.

THE SULFANYLUREAS. When Janbon[13] made his astute observation in 1942, that the administration of an isopropylthiodiazole derivative of sulfonamide to patients with typhoid fever, produced symptoms simulating the hypoglycemic syndrome, little did he realize that about a decade later, his discovery would stimulate world-wide studies of the drug. He set out to find an effective and prolonged antimicrobial therapy in typhoid fever and as a consequence found a drug with an hypoglycemic action. This serendipity resulted in thousands of experimental and clinical publications.

That this is the case is not surprising as scientists have been searching for an insulin-like substance that could be administered orally and Janbon's discovery aroused high hopes that such a substance was in the offing. It was hoped that it would have other insulin-like properties, in addition to its power of lowering the blood sugar, and if this could be established, the treatment of the diabetic would be simplified and the use of injections eliminated. To be sure, these ideas and hopes were not new.

Loubatieres[15], an associate of Janbon, studied the effects of some sulfanylureas in diabetic animals and patients and from his early and well planned experiments he stated: "It is logical to assume that such hypoglycemic agents could eventually be used in the treatment of certain forms of diabetes." Though this statement was made in 1946 he did not begin his clinical trials until 1955. At about the same time Franke and Fuchs[8], also Bertram and his associates[4] reported their observations on an active oral hypoglycemic drug BZ 55. This drug, too, was discovered as a consequence of other studies. After some trials, it soon became available commercially as carbutamide. Its analogue, tolbutamide, was also being studied. Thus physiologists, pharmacologists, biochemists and clinicians became engrossed in the study of the two available sulfanylureas and thousands of publications have eppeared all over the world describing every conceivable experimental and clinical approach in an attempt to understand their mechanism of action and to utilize that understanding in the clinical application. It is not the purpose, nor would it be practical, to mention all the experimental data, and though illuminating, they have been

contradictory. This is understandable, as various species of animals, various techniques and different approaches were used by investigators. Indeed, the literature reveals experiments from simple metabolic studies to the most complex, enzymatics, micrometabolic and tracer studies. It can be assumed, therefore, that the results of all these investigators are valid and their contradictory nature must be explained by differences in the technological approaches. It seems that almost every facet of carbohydrate metabolism had been explored with these agents, and studies on fat metabolism have been also recorded.

The clinical data, with which this review is concerned, are not as sound as the experimental. This, too, is understandable as conclusive clinical evidence is hard to come by, since ideal controls are seldom possible. One can not create ideal experimental conditions in the patient as in the test animal. Furthermore, no clinician feels justified in taking risks which may jeopardize the patient. Also, close observations of many patients under hospital conditions have proved impractical because of the time loss and expense. All these factors have contributed to a great variety of experimental conditions. Some reports deal with patients studied in the outpatient departments, others deal with private office patients, still others report studies on hospital services both general and metabolic. Reports deal with observations of groups of diabetic patients from (Bruce[3]) 3 to as many as 1,030 (Mehnert, Carnerini-Davelos and Marble[17]).

Criteria for satisfactory control were not uniform and were set up arbitrarily by each observer. There was considerable variation in the diets, the total caloric intake varying from 1500 to 3000. Furthermore, some of these menus were in the hospital where the diets were weighed, while the ambulatory patients estimated their food prescriptions and no doubt took liberties at times. No scientist trained in experimental methods would even make an attempt to draw conclusions from results obtained under so many variable conditions. Yet the clinician accepted them and is using the sulfanylureas quite freely and extensively (over 15,000 patients up to midsummer of 1957) (Goldner and Weisenfeld[9]) in the treatment of diabetes and reports that *satisfactory control* can be achieved in a selected group of diabetic patients. Since carbutamide was withdrawn from the market in this country, tolbutamide became the only sulfonylurea available commercially and the discussion will be confined to its clinical use. It is dispensed in 0.5 gm. tablets under the name of Orinase.

What have we learned about this drug to date from the prodigious amount of work that had been done in the relatively short period of nearly 3 years? Only knowledge in which there has been agreement will be presented. 1) Tolbutamide *lowers* the blood sugar and reduces the glycosuria in *some*, but not all diabetics. 2) The maintenance dose is from 0.5 to 1.5 gm. daily, with priming dosages of 3 gm. the first, 2 gm. the second, and 1 gm. the third day. 3) It is ineffective in juvenile diabetes. 4) It has a small incidence of toxicity, chiefly dermatoses and leukopenia. Neither has been reported as serious and both clear when the drug is discontinued. 5) Infrequently, the drug may lose its effectiveness, after a period of use.

It is generally agreed among clinicians, that the middle-aged, nonobese diabetic, who consumes an adequate diet and requires about 20 to 40 units of insulin daily to be controlled, nearly normal blood sugar and freedom from or minimal glycosuria, is the most ideal

candidate. The majority of reports claimed success with this segment of the diabetic population and more patients in this category demand the drug. Whether or not to yield to this demand is a dilemma which has been discussed admirably by Goldner and Weisenfeld[9] in their cogent paper. Furthermore, their recommendation for the appropriate patient for treatment with tolbutamide will prove most helpful. They write: "There is a difference between successful clinical trials and clinical indications for a drug. The purpose of clinical trial is to establish the widest possible parameter of effectiveness. The clinical indications, on the other hand, are those conditions where a particular drug is needed or specifically effective and advantageous." With this sound premise they divide the "ideally" suited diabetic patients into 5 categories. They rule out one segment which can be managed by dietary means only. They do not recommend combining tolbutamide with insulin, as in their opinion this would complicate the treatment. The third group of diabetic patients in whom tolbutamide effect is transitory is also not suitable. Then the very small group in whom side effects appear should be eliminated, leaving a group in whom tolbutamide can be used, but they add that even in this group "the indication is not a strict one, but rather one of choice." This is sound philosophy and, until newer facts are learned about tolbutamide, should be the guide for oral therapy of diabetes.

Tests have been devised to learn whether or not the patient will respond to the use of the drug. If the patient had been on insulin therapy, the insulin is discontinued for 24 to 48 hours prior to the test. The patient's fasting blood sugar is determined, he is given 3.0 gm. of tolbutamide, and another blood sugar is done, 3 hours thereafter. At the Joslin Clinic a fall of 20% of the initial blood sugar value is considered positive (Joslin[14]). This has been revised so that a blood sugar level of 110 mg. per 100 ml. three hours after the tolbutamide is the deciding figure.

Duncan and his associates[7] have employed 2 other techniques. The first requires 15 days, divided into 3 consecutive 5-day periods. The insulin dosage is reduced prior to the test. The first 5 days are used as the base line, during which time the total 24-hour glucose excretion is recorded as well as a fasting and a two-hour postprandial blood sugar determination. The second period is used as the test with a 1 gm. dose of tolbutamide given every 6 hours. No drug is given during the third period. The diet is constant throughout the experiment. A fall in the blood sugar and a quantitative decrease of the glycosuria are considered positive evidence of effectiveness.

Another approach is to divide a definite dietary prescription into 12 equal portions. A portion is eaten every 2 hours. A lowering of the blood sugar after 2 gm. of tolbutamide with such repeated feedings, was considered positive. Still another test is based on the principle of whether or not tolbutamide will prevent ketonuria within 8 hours after the insulin had been discontinued, the diet remaining the same.

It may be pointed out that none of these tests is absolute, as some patients will not respond to an immediate blood sugar lowering effect, but in a week or more show the drug's hypoglycemic effects. As a result some clinical investigators have abandoned all tests. They prescribe the drug, observe the patient for 2 to 3 weeks, and make their decision thereafter.

There is thus available a drug, tolbutamide which has the pharmacological property of lowering the blood sugar in a small group of diabetics.

The drug has also been used in various species of animals experimentally in the laboratory, where many facets of the mysteries of carbohydrate metabolism have been explored. As a laboratory tool it has been of great usefulness and may shed considerable light upon some of the unknowns of diabetes. Clinically, it has limitations and as a therapeutic agent it leaves much to be desired.

Summary. Of the substances used for the treatment of diabetes, the insulins and the sulfanylureas, the former has a wider field of usefulness and is the remedy of choice. Insulin is truly a miraculous tool. Not only does it save life, but makes living endurable. It has *no* contraindications except in the rare cases of allergy and this obstacle can be treated successfully. It can be used with satisfactory effectiveness in *all* types of diabetics, young or old, and its only hazard is a reaction due to overdosage, relative or absolute. Another minor drawback is its method of administration by hypodermic injection. There are various insulins on the market and though the physician has a wide choice, he will do well if he limits himself in most cases, to the fast-acting preparation (crystalline or regular insulin) and to an intermediary one. With two such preparations the entire field of diabetes, young and old, ambulatory, and complicated by either a medical or surgical condition, can be managed successfully. There are no limitations, and it can be stated dogmatically that insulin is truly antidiabetic. The sulfanylureas *are* limited in the area of diabetic therapy, as they are applicable only in a *selected* group of patients. They can be given by mouth and lower the blood sugar. Though there are many disagreements as to what other pharmacological effects this drug exhibits, the conclusion of all clinicians and other investigators is unanimous as to their hypoglycemic property. How this is done is still unknown. It must be pointed out, that though they are hypoglycemic and though they may eliminate the symptoms of diabetes, they are not antidiabetic as is insulin. There is no conclusive evidence that they will effect a positive nitrogen balance, nor will they arrest ketogenesis, two facets of the diabetic complex that respond readily and definitely to insulin. This implies that the treatment of diabetes and lowering the blood sugar are sequential or coincidental, but certainly not synonymous, anymore than lowering the white count in leukemia corrects the underlying pathological disturbance in that disease. Until more is known of the sulfanylureas, their use must be judicious and the physician must be prepared not to expect too much from them.

All new drugs must have a beginning and the introduction of the sulfanylureas may be the beginning of a new era in diabetic therapy. There are many oral preparations being studied and it is hoped that one will be found to possess truly insulin-like action. At present, however, one must be cautious and guarded when using the sulfanylureas, as we have still to learn a great deal about them, not only their mechanism of action, but about their ultimate place in the treatment of diabetes.

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RADIOLOGY

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THE ROENTGEN SIGNS OF SYSTEMIC DISEASE IN THE SKULL

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DURING the past 25 years, there has been a sustained interest in localized diseases of the brain and their effects on the cranium. With the development of pneumoencephalography and cerebral arteriography, the radiological assessment of these lesions has improved rapidly. On the other hand, the effects of systemic diseases on the skull have largely been neglected. One of the persisting sources of diagnostic error has been the failure to recognize certain skull lesions as manifestations of a generalized disease. In this review, a discussion of the systemic diseases has been attempted, according to the radiological findings which they produce in the skull. Diseases affecting only the skull or the nervous system have been omitted. The literature on this subject has consisted largely of studies of single entities or case reports. An excellent classification of general affections of the skeleton was given by Fairbank[63].

Systemic Abnormalities Affecting the Growth of the Skull. INCREASED INTRACRANIAL PRESSURE IN CHILDREN. Any disease which causes an increase in intracranial pressure before the sutures close may cause generalized enlargement of the cranium. Spreading of the sutures, however, is uncommon after the age of 12 years. Marked increase in cranial size occurs only in diseases dating from infancy. The increased pressure then frequently causes a generalized thinning of the calvaria and retards closure of the fontanelles. In older children, the convolutional markings of the inner table of the calvaria become abnormally prominent. The sella turcica usually fails to show any alteration in early childhood. The more important systemic causes of increased pressure with cranial enlargement are: neuroblastoma, leukemia, lead encephalopathy, nephritic encephalopathy, tuberculous meningitis or tuberculoma, Hurler's syndrome, osteopetrosis[17], primary hypoparathyroidism, infantile toxoplasmic encephalomyelitis[26,70,126], torula meninoencephalitis[133], and hydatid disease[125].

MICROCEPHALY. An abnormally small cranium without alterations in contour may be accompanied by hyperostosis of the entire calvaria and base, or involve only the base of the skull. The common causes of microcephaly are:

mongolian idiocy, cretinism, infantile toxoplasmosis[26] or torulosis[133], and cytomegalic inclusion disease[153].

EXTERNAL DEFORMITIES OF THE SKULL. Any disturbances in the shape of the skull must date back to the period of active growth of the cranium, that is, to the first two years of life. Certain deformities are nonspecific. Any condition causing prolonged recumbency or calvarial softening frequently results in flattening of the occiput or asymmetry. An upward and outward slanting of the orbits is frequently seen in many skull deformities, especially with enlargement of the cranium. It may be especially marked in chondrodystrophia calcificans congenita[9].

Asymmetry of the cranium frequently results in moderate hyperostosis of the calvaria, elevation of the orbit, wings of the sphenoid and petrous ridges, and over-development of the paranasal sinuses on the smaller side. These findings have been described in unilateral cerebral atrophy, craniostenosis, congenital hemihypertrophy, and torticollis or scoliosis[94]. They have also been found following severe meningitis of early childhood[107]. In neurofibromatosis[13], asymmetry of the orbits, sphenoid wings, petrous ridges and calvaria frequently occurs; the middle cranial fossa on one side is sometimes abnormally deep. The majority of children with Sturge-Weber angiomatosis have an asymmetric calvaria, particularly in the occipital region, due to underlying cerebral atrophy.

Abnormal shortening of the base of the skull in the presence of microcephaly has been described with both cretinism and mongolism. Skull changes associated with cretinism, however, have been greatly over-emphasized in the past. The majority of cretins have normal appearing skulls except for a general delay in development. In mongols, the sutures and fontanelles are frequently abnormally wide. The floor of the anterior cranial fossa may be steep and the cribiform plate is often shorter and at a higher level than usual. There may also be slight hypoplasia of the facial bones.

Several conditions are associated with deformity of the skull accompanied by a disproportionate increase in size. In cleidocranial dysostosis, there is usually brachycephaly, depression of the bridge of the nose, prominent frontal and parietal bosses and shortening of the base of the skull[57]. The ossification of the vault is frequently retarded with wide fontanelles and sutures, poor pneumatization of the sinuses and mastoids, and somewhat hypoplastic maxillae. In achondroplasia, the basal portion is usually shortened due to lack of growth of the spheno-occipital synchondrosis resulting in a steep clivus. The foramen magnum is often small and funnel-shaped. The posterior cranial fossa is shallow[104]. The calvaria may be enlarged, and the sinuses may be over-pneumatized with osteogenesis imperfecta. The enlarged cranium is frequently accompanied by bulging of the temporal regions.

Dolichocephaly accompanied by frontal and parietal bossing has been described in arachnodactyly as well as in rickets of long duration.

In gargoylism (Hurler's syndrome, dysostosis multiplex) the enlarged cranium frequently bulges in the temporal region and the vertex is narrowed[172]. The enlarged cranium of hereditary anhydrotic ectodermal dysplasia is frequently accompanied by frontal bossing and thickening of the inner table.

PREMATURE SYNOSTOSIS OF CRANIAL SUTURES. Premature closing of the sutures frequently prevents the growing intracranial contents of infancy from

expanding, producing increased intracranial pressure and increased digital markings of the calvaria. Hypoplasia of the mastoids and sinuses is frequently associated. If a suture becomes closed on one side, asymmetry of the cranium results. Most cases of craniostenosis are idiopathic, but a small proportion are associated with the following generalized abnormalities or diseases: cerebral atrophy, hydrocephalus, mongolism, osteogenesis imperfecta, hypogonadism, hypopituitarism, severe idiopathic infantile hypercalcemia[172], familial vitamin D resistant rickets[35]. In arachnodactyly[105], the coronal suture of one side has sometimes become fused resulting in asymmetry and deepening of the corresponding middle cranial fossa. "Tower skull" (Turmshadel) produced by premature closure of the coronal sutures has sometimes been associated with syndactylism of the upper extremities[79,106], or with congenital hemolytic icterus[64,174].

WORMIAN BONES. Sutural bones are frequently seen as a normal variation especially in the lambdoid suture. However, a large number of these bones sometimes occurs when the ossification of the calvaria is markedly retarded, especially in cleidocranial dysostosis, osteogenesis imperfecta, and also in a few instances of cretinism, cerebral atrophy, and severe cyanotic congenital heart disease.

Rarefying Lesions of the Cranium. The diseases associated with generalized rarefactions of the skeleton are usually subdivided into an "osteoporotic group" due to defective formation of bone matrix, and an "osteomalacic" group due to a defective mechanism of calcification[1]. Any of these diseases may effect the skull. For practical purposes, they may be divided into those of childhood and adulthood, although the two groups are not mutually exclusive.

GENERALIZED RAREFACTIONS OF THE SKULL IN CHILDREN. Rickets of any type (nutritional, vitamin D resistant, Fanconi's syndrome, secondary to biliary atresia or celiac disease) may produce general demineralization of the skull. The vault is usually thinned, but is sometimes thickened. When thinning occurs in infancy, the clinical sign of craniotabes may be elicited. Delay in closure of the anterior fontanelle is seen only in severe cases. Frontal and parietal bossing is a rather late change. In a few instances of severe rickets of long duration, increased convolutional markings have been observed. These skull changes have occasionally been present in the absence of detectable changes in the long bones. However, in the majority of cases, the long bone manifestations are more marked than in the skull. When only minimal long bone lesions are present, the skull may be negative. When there is complete failure of skeletal growth, osteomalacia may be seen in childhood without rachitic change[106]. This has been observed in severe hepatic disorders (cirrhosis, biliary atresia, hepatolenticular degeneration, glycogen storage disease and galactosemia).

In renal osteodystrophy of childhood, the skeletal changes are of two different types. Firstly, the changes in the long bones and cranium may be identical to those of ordinary rickets[32]. Rachitic long bone changes are not infrequently observed with a normal appearing skull[44]. In the second or "woolly" type, a granular decalcification and patches of increased density in the cranium produce a Paget-like picture. The "woolly" areas are located chiefly in the outer table. There is often an increased thickness of the calvaria and the differentiation of the tables from the diploe tends to be lost[138]. This pattern

of generalized mottling is usually somewhat coarser than the pattern seen in adult primary hyperparathyroidism.

The generalized osteoporosis of scurvy affecting the skull is much less common than rachitic changes. Scorbutic subperiosteal hemorrhages in the cranium are rarely seen. Although changes in the long bones are regularly observed in hypervitaminosis A, the findings in the skull (similar to rickets) are rarely observed[3]. In hypophosphatasia[95,149], marked demineralization is usually noted, in addition to marked retardation in ossification of the bones of the vault. Juvenile diabetics suffering from prolonged acidosis may develop generalized osteoporosis which includes the vault. In hypervitaminosis

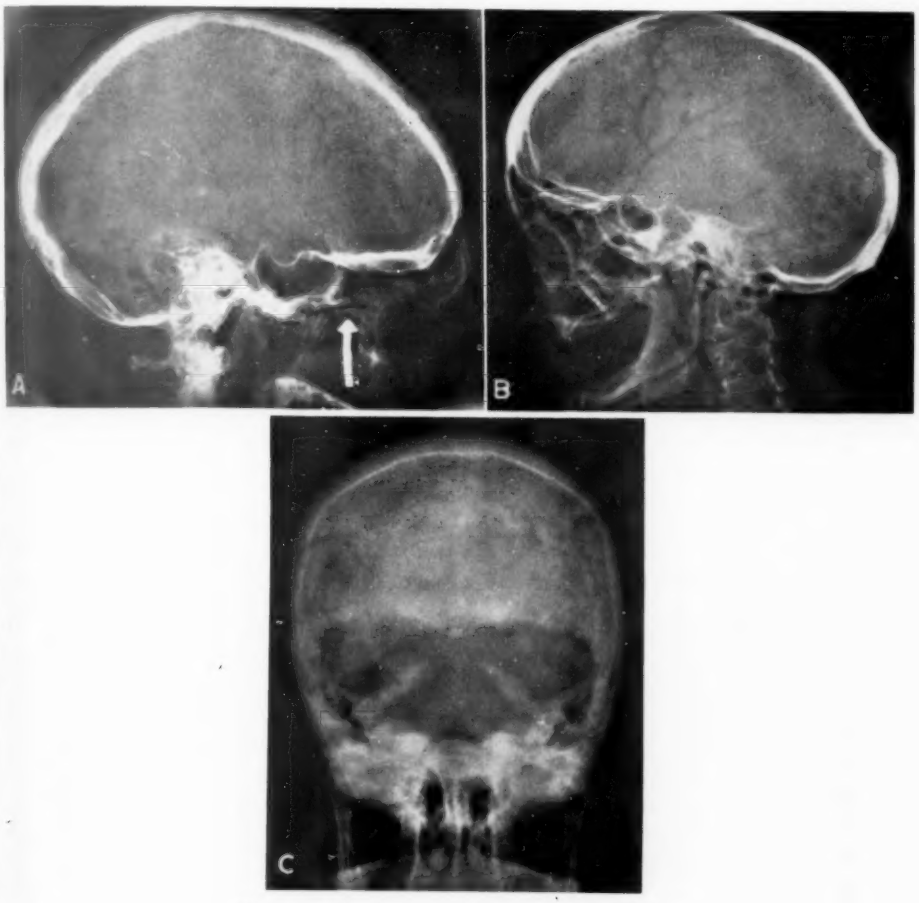


Fig. 1.—Types of rarefaction of the skull
(A) Malacic pattern of primary hyperparathyroidism: coarse speckled rarefaction of the calvaria without thinning and localized "osteoporosis circumscripta" of the temporal regions. (B) Porotic pattern of osteogenesis imperfecta: generalized rarefaction with thinning of the calvaria. Secondary basilar impression accompanied by mild backward rotation of the atlas. (C) Osteoporosis circumscripta of the occiput: early phase of Paget's disease. Bilateral calcification of dentate nuclei.

D and in the rare condition, oxalosis, granular osteoporosis of the cranium has been seen[53].

Occasional instances of acute leukemia without evidence of bone destruction, have had generalized osteoporosis. This apparently tends to occur under prolonged therapy with folic acid antagonists[99] or cortisone.

Certain osteochondrodysplasias are accompanied by generalized osteoporosis of the cranium. In osteogenesis imperfecta particularly, extreme thinning of the vault is often present. Sometimes even skull fractures, produced by little or no trauma, are seen. The facial bones usually appear normal. In cleidocranial dysostosis, mild generalized porosis usually accompanies the retarded ossification and thinning of the cranium. There is also poor pneumatization of the sinuses and mastoids.

In the hemolytic group of anemias, the majority of cases have a normal appearing skull[83]. The skull changes in sickle cell anemia, present in less than half of the cases[58,116], are usually better demonstrated in children than in adults. Contrary to many textbook descriptions, the most common radiological finding in the skull is osteoporosis. The calvaria may be either thinned or increased in thickness. The thickening is usually due to a wide radiolucent diploe accompanied by thin and indistinct tables[152]. In congenital hemolytic icterus or spherocytosis, changes similar to those of sickle cell anemia are seen[34], but less frequently.

GENERALIZED RAREFACTION OF THE ADULT CRANIUM. In primary or secondary hyperparathyroidism, the diffuse rarefaction usually has a granular stippled pattern with blurring of the inner and outer tables[1,22,146]. There is usually no decrease in thickness of the calvaria[1]. Only a small proportion of cases exhibit single or multiple cystic lesions, due either to fibromatous areas or to "osteoclastomas"[174]. Scattered areas of bone condensation appear at a later stage producing a "woolly" or "pagetoid" picture. It must be borne in mind that only about one-third of all cases of hyperparathyroidism exhibit radiological changes in the skeleton[146]; furthermore, a granular stippled pattern to a certain degree may be seen in normal skulls[22]. Loss of bone density has been observed in only a few cases of hypoparathyroidism[71].

Osteomalacia in the adult may be due to a variety of causes, such as vitamin D deficiency, resistance to vitamin D, steatorrhea, biliary fistula, prolonged jaundice, renal acidosis, and idiopathic hypercalcuria. The demineralization of the cranium is frequently accompanied by an increase in thickness of the diploic layer and thinning of the tables.

Diffuse cranial rarefaction may be associated with generalized osteoporosis from the following causes: senile or postmenopausal osteoporosis, Werner's syndrome (adult idiopathic progeria)[142], hyperthyroidism[76], hypervitaminosis D, hypopituitarism, Cushing's syndrome, ACTH or cortisone therapy, gastrointestinal fistula[95] or malnutrition. In osteoporosis associated with hypogonadism (eunuchoidism or ovarian agenesis) the osseous changes usually do not begin until puberty[1]. Porosis is observed in a minority of cases of acromegaly. In myelomatosis, diffuse rarefaction of the skull is occasionally seen, rather than the more familiar multiple areas of destruction. When skeletal lesions are present with urticaria pigmentosa, there is usually diffuse or pseudo-cystic rarefaction of the vault, especially of the inner table[115,160], contrasting with the widespread sclerosis and coarse trabeculation of the spine and extremities.

LOCALIZED RAREFACTION OF THE CALVARIA. Biparietal symmetrical thinning

has not infrequently been observed in the posterior parasagittal areas[60]. The margins of the lesions are often well demarcated and the external table may show marked thinning along its external contour. Although some cases are said to be developmental in origin, the lesions have been seen associated with generalized senile osteoporosis elsewhere in the skeleton[60]. Localized rarefaction of the middle cranial fossa, sometimes with thinning and localized bulging has been observed with neurofibromatosis or cerebral agenesis[31]. In a minority of cases of Cushing's syndrome, decalcification of the vault may occur in multiple "pseudo-metastatic" patches with the intervening bone of normal density[93]. In rare instances of osteomalacia[63,174] and sickle cell anemia[50] mottled radiolucent areas have been observed simulating the punched-out lesions of myeloma or metastases.

Osteoporosis circumscripta is a large asymmetric and irregular area of rarefaction of the calvaria, usually due to Paget's disease, but rarely due to hyperparathyroidism[174,193,199], or fibrous dysplasia[174]. From 22% to 36% of all Paget's lesions of the skull begin as osteoporosis circumscripta[49,143,162]. This is regarded as the early or monophasic stage of the disease, later to be replaced by the second biphasic stage or "woolly" pattern of alternating sclerosis and rarefaction, and the third or last stage of predominant sclerosis[162]. The demineralization first begins in the diploe[78] as a result of increased vascularity, adjacent to the normal diploic vascular channels; thinning of the outer table then precedes that of the inner table. The frontal region is probably the most common site. The lesion may be the first manifestation of Paget's disease throughout the skeleton[12]. It may, however, occur in combination with more advanced sclerotic or hyperostotic lesions of the face or calvaria.

BASILAR IMPRESSION AND PLATYBASIA. These frequently coexisting conditions may be primary or developmental in origin, or secondary to any condition causing rarefaction and softening of the base of the skull. Basilar impression (invagination of the occiput by the upward pressure of the cervical spine) is more important to consider than platybasia (flattening of the basal angle of the skull). A significant degree of basilar impression may be responsible for neurological symptoms, such as the Arnold Chiari syndrome. With the secondary form of the lesion, the occipital condyles are the first structures to become displaced upwards; platybasia is, therefore, not present in the early phase. In lateral films of the skull, the atlas becomes rotated so that its anterior arch migrates upwards and backwards[16] and the odontoid process of the axis also becomes displaced upwards.

The commonest cause of the condition is Paget's disease, especially in the form of osteoporosis circumscripta of the occiput[16,143]. The lesion has also occurred not infrequently with prolonged rickets or osteomalacia[140], hyperparathyroidism, osteogenesis imperfecta, cleidocranial dysostosis, senile osteoporosis, and Schüller-Christian's reticuloendotheliosis[5]. It is rather infrequently seen in the osteochondrodysplasias and in cretinism.

PROMINENT VASCULAR MARKINGS OF THE CALVARIA. The observation of prominent or asymmetrical vascular markings is of little diagnostic value, because of marked normal variations[108]. Unusually prominent vascular markings classically occur with meningiomas, but have been observed in a few generalized diseases such as Sturge-Weber angiomatosis, Maffucci's syndrome (multiple osteochondromata with su-

perficial hemangiomatosis[130], in adult cases of gargoylism[173] and in severe cyanotic congenital heart disease associated with marked hyperplasia of the bone marrow. Increased vascular markings can probably be produced by any prolonged increase in intracranial pressure.

Destructive Cranial Lesions. SINGLE OR MULTIPLE LYTIC LESIONS OF THE CALVARIA. Occasionally, normal but large vascular "lakes" in the diploe may produce single or multiple radiolucencies simulating real destructive lesions. Frequently however, one or more vascular channels may be seen entering the suspicious areas, and their size does not change on serial films.

A variety of chronic infectious granulomas may produce single or multiple areas of erosion. Although syphilis and tuberculosis are still the commonest lesions, their incidence has decreased rapidly. Multiple small lytic lesions with ill-defined margins may occur in congenital, secondary, or tertiary lues[10]. Both tables are usually involved in addition to the diploe, and there may be overlying soft tissue nodules of the scalp[123]. The anterior and lateral portions of the calvaria are more commonly involved than the posterior. The margins of the lesions may occasionally show increased trabeculation[123], or small areas of sequestration[159]. The areas have temporarily become larger following initiation of antiluetic penicillin therapy. Rarely, large serpiginous "worm-eaten" defects may appear, simulating the lesions of pyogenic osteomyelitis. These may contain rather large sequestra or patches of sclerosis. Lesions similar to those of lues are rarely observed in tertiary yaws.

Tuberculous lesions of the vault may be well demarcated areas of pure destruction[2,183] or they may occasionally have central minute sequestra ("bone sand"). Other areas of involvement in the axial skeleton are almost always present, and frequently appear at the same time. About 85% of the skull lesions select the frontal or parietal bones, and half of them are solitary[121]. They are more commonly seen during childhood[183]. Only about half of the cases have detectable pulmonary lesions[120]. Although the earliest erosion of the calvaria begins in the diploe, the tables are usually involved more extensively[189]. In infants, only the external table may be eroded, and accompanied by soft tissue swelling (Pott's puffy tumor). Rarely, there is extensive serpiginous destruction, as in pyogenic osteomyelitis. There is sometimes hypercalcemia and hypercalcinuria. With streptomycin therapy, the areas usually show signs of healing. In leprosy, calvarial lesions are rare, even in patients with long-standing disease.

Lytic lesions due to brucellosis[113] have been described.

The fungus granulomas of torulosis (cryptococcosis), blastomycosis and coccidioidomycosis have produced circumscribed osteolytic areas which are frequently disseminated throughout the skull[38,124,187]. These lesions contrast with those of actinomycosis, which produces only localized lesions extending by direct invasion. Coccidioidal granulomas are not uncommon in endemic areas[124]. They are more common in adults, and the Negro race is apparently more susceptible. Only half of the cases have associated pulmonary lesions. There is frequently an overlying soft tissue nodule[187], but progression to abscess formation or ulceration is unusual. The lesions may progress more rapidly than tuberculous granulomas.

A few benign tumors or tumor-like lesions may produce cystic areas in the calvaria, associated with other skeletal lesions. In monostotic or polyostotic fibrous dysplasia, lytic lesions,

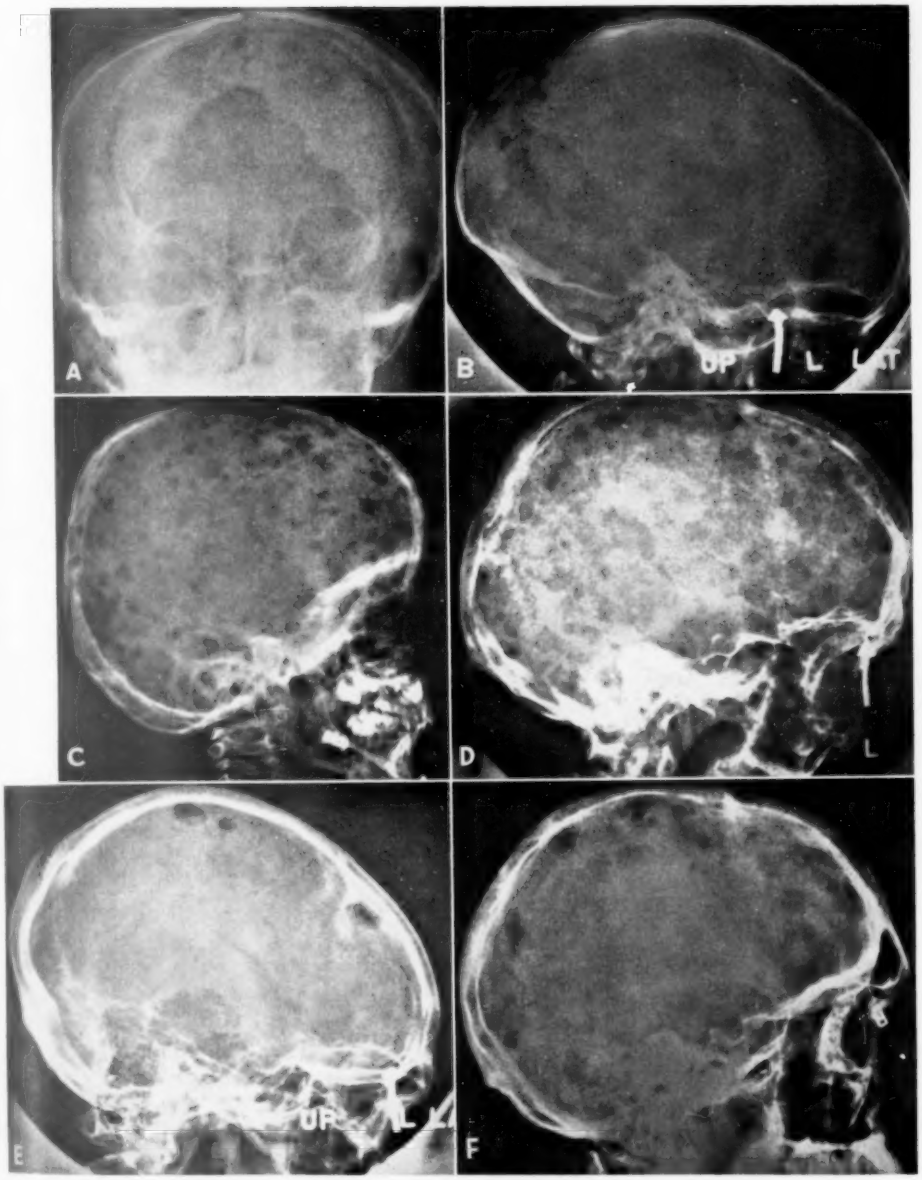


Fig. 2.—Destructive calvarial lesions.

(*A*) and (*B*). Large occipito-mastoid defect due to neurofibromatosis accompanied by large external soft tissue mass. Marked asymmetry of calvaria, orbits, sphenoid wings, and petrous ridges seen on frontal view.

(*C*) Schüller-Christian's reticuloendotheliosis in young child. Multiple small oval and irregular osteolytic areas throughout calvaria. Minimal sclerosis and thickening of anterior base of skull.

(*D*) Myelomatosis: Multiple small destructive lesions coalescing into a diffuse "worm-eaten" pattern throughout diploic layer of calvaria.

(*E*) "Punched-out" areas of destruction due to tuberculous granulomas.

(*F*) Multiple calvarial defects due to widespread hemangiomatosis, without cutaneous involvement.

usually with sclerosis of the margins, are often seen in the calvaria, especially in the parietal bones[43,155]. These contrast with the pagetoid lesions of the calvaria or the purely sclerotic lesions in the base of the skull and facial bones. Patients with neurofibromatosis have had skeletal changes in 7%[63] to 30%[92]; the calvarial areas of destruction vary greatly in extent; sometimes large map-like areas of erosion are encountered. Benign systemic hemangiomatosis (hemangiohamartoma) often produces multiple areas of erosion in the calvaria. The frequency of skull involvement is second only to that of the spine[151]. The lesions are often located in the parietal bones and there may be bulging of the tables. Some of the lesions may have a sclerotic element. This entity is more probably a malformation rather than a true neoplasm. It is frequently difficult to diagnose, because the widespread osseous lesions are often not accompanied by cutaneous lesions[137].

Malignancies are well known as important causes of multiple punched-out defects of the vault. About 13% of all patients with lymphomas have osseous involvement postmortem, but only 12% of these occur in the skull[36]. The lesions are encountered in Hodgkin's disease, in lymphosarcoma, especially in young adults, and rarely in myelogenous leukemia[33,192]. Malignant melanoma[165] not infrequently metastasizes to the vault. Primary reticulum cell sarcoma of bone involving the skull is extremely rare[37], but about one case in 6 eventually metastasizes to the skull[100]. The familiar discrete multiple punched-out lesions of myeloma have perhaps been over-emphasized in textbooks, as they are seen in only a minority of patients[110]. Frequently, the calvaria shows only vaguely defined areas of rarefaction. Skull radiographs have frequently been negative in the presence of well defined destructive lesions elsewhere in the skeleton. The cranial lesions are sometimes extremely small but close together producing a widespread "worm-eaten" appearance. Rarely, myeloma occurs as a solitary lesion (solitary plasmocytoma) producing a cystic or multi-cystic expansion of the vault[201]. The commonest cause of multiple areas of cranial destruction, metastatic carcinoma, usually arises from primary tumors of the breast, lung, kidney, prostate or thyroid.

LYTIC CALVARIAL LESIONS USUALLY SEEN IN CHILDHOOD. Destructive lesions in children are usually due either to a liporeticulosis, or malignancy. Skull lesions are present in over 90% of children with Schüller-Christian's reticuloendotheliosis (histiocytosis X) and the calvaria is involved in 80%[5]. Identical lesions, both from a radiological and pathological standpoint are encountered in eosinophilic granuloma. Sharply demarcated, small oval or large irregular "geographic areas of destruction are usually seen. They readily enlarge or regress. There are often palpable soft tissue nodules in the overlying scalp. In the healing phase, the margins of the lesions become indistinct. The healing frequently becomes so complete that the site of previous lesions cannot be detected radiologically. The duration may vary from a few weeks to many years[88]. Multiple minute areas of destruction, producing a speckled appearance are rarely seen in Gaucher's disease (kerasin liporeticulosis)[63]. Destructive lesions are extremely rare in Niemann-Pick's disease (lecithin liporeticulosis)[139].

The commonest destructive lesion of the cranium in childhood is neuroblastoma[166], since about 20% of all children with this disease have skull metastases. Leukemic destruction is less common[39]. The lesions are usually indistinguishable in the two conditions. Minute

areas of erosion are frequently seen with a tendency to concentrate at the suture edges. This appearance may closely simulate a simple spreading of the sutures[86]. The areas may be larger producing a "myelomatous" picture. Since Ewing's sarcoma of bone is either closely related or identical with neuroblastoma histologically, it is not surprising that it may produce identical roentgenographic findings in the cranium[185]. Metastatic embryonal rhabdomyosarcoma from a primary muscle tumor usually in the head and neck[20] also may produce fine destructive lesions identical with those of neuroblastoma or leukemia.

DESTRUCTION OR ENLARGEMENT OF THE SELLA TURCICA. Numerous localized erosive lesions of the sella may produce hypopituitarism and sometimes diabetes insipidus, as follows[175]: pituitary adenomas, craniopharyngioma, chiasmal or hypothalamic gliomas, meningioma, neurofibroma, chordoma, teratoma or dermoid, pinealoma, and cholesteatoma. Large aneurysms of the internal carotid artery may also cause partial or complete sellar destruction. Erosion may also take place from direct extension of nasopharyngeal or sphenoid sinus malignancies. From 2% to 12% of sellar erosions are metastases from distant malignancies[78]. In Schüller-Christian's disease, radiologically visible destruction of the sella is unusual, despite the frequent involvement of the hypophyseal stock and hypothalmus producing diabetes insipidus[5]. Varying degrees of unilateral or bilateral destruction may be seen in neurofibromatosis[13,92].

In acromegaly and pituitary giantism the sella is usually but not always expanded due to the eosinophilic pituitary adenoma. In Cushing's syndrome, there is usually just atrophy of the posterior clinoid processes and dorsum sellae, in keeping with the generalized osteoporosis. True destruction or enlargement of the sella is relatively rare.

An almost invariable finding of Hurler's syndrome (gargoylism) is an enlarged pituitary fossa which is elongated and shallow, or shoe-shaped. The clinoid processes may be poorly developed. This sellar deformity is an integral part of the dysplasia and is not due to pressure erosion[173,202]. The sella may also be expanded in cretinism[17] and in Maffucci's syndrome (dyschondroplasia with angiomatosis)[104].

DESTRUCTION OF THE MASTOIDS AND PETROUS TEMPORAL BONES. In the differential diagnosis of the causes of destruction of the temporal bone, such localized lesions as mastoiditis, cholesteatoma, hemangioma, and glomus jugulare tumors are the most important. Destruction may also occur as a result of direct spread from a primary carcinoma of the middle ear, a nasopharyngeal tumor, or a cerebello-pontine angle tumor.

In children, tuberculous mastoiditis is still not uncommon; it is usually accompanied by a pulmonary lesion. Mastoiditis due to histoplasmosis is rare. One of the commonest causes of osseous destruction in childhood is Schüller-Christian's disease; discharge from the ear is the commonest presenting complaint in this syndrome[5].

Fibrous dysplasia of the petrous or mastoid portions of the temporal bone is not unusual, but the lytic areas are usually accompanied by other areas of sclerosis or hyperostosis. Erosions of the internal auditory canal may occur in acoustic neuromas associated with neurofibromatosis. Patients with Paget's disease not infrequently have apparent destruction of the petrous temporal bones, but this on careful examination is merely an appearance due to extreme rarefaction. Metastatic carcinomas and lymphomas may involve the temporal bone.

DESTRUCTION OF THE PARANASAL SINUSES. In primary lesions causing destruction of the sinuses, such as carcinoma, fibrosarcoma and osteomyelitis, the maxillary sinus is the most common site. In generalized diseases likewise, the maxillary antra are most commonly involved. The erosion at this site may occur from metastatic carcinoma, particularly from primary breast lesions, from malignant melanoma[165], plasma cell myeloma. Mid-line lethal granuloma may destroy the sinus walls, nose and orbits. It may be a localized disease, or be associated with Wegener's necrotizing granulomatosis[66]. In this entity, the ulcerating granulomatous lesions of the upper respiratory tract are associated with pulmonary nodules, focal glomerulonephritis and a generalized angiitis resembling periarteritis nodosa. Sinus destruction may rarely occur from direct extension of intracranial tumors, such as chromophobe pituitary adenomas and meningiomas.

In children, marked mucous membrane thickening of the sinuses secondary to Schüller-Christian's reticuloendotheliosis is not unusual, but actual destruction of the sinus walls is rarely seen[5].

DEFECT OF THE ORBIT. In adults, destruction of the orbital walls is encountered in malignant melanoma or metastatic carcinomas, and in children, from retinoblastoma (neuroblastoma) or Schüller-Christian's disease. In this latter condition, one third of all patients have orbital changes[5].

In neurofibromatosis, defects in the superior wall of the orbit, either developmental or secondary to pressure erosion, often result in pulsating exophthalmos[13,92]. There may also be marked unilateral enlargement of the orbit or optic foramen, or elevation or depression of the involved orbit. Defects of the orbital rims have been described with cleidocranial dysostosis[154].

DEFECTS OF THE NASAL BONES. The nasal bones may be eroded in congenital or tertiary lues[164], or rarely in sarcoidosis[91], usually with an overlying subcutaneous soft tissue lesion. The nasal bones may be congenitally absent or hypoplastic in mongolism, cleidocranial dysostosis[139], chondrodystrophia calcificans congenita[9] or infrequently in cretinism.

Cranial Lesions with Bone Production. A large number of generalized diseases is capable of causing bone production in the skull. A clear distinction must be made between "hyperostosis" in which the skull is increased in thickness, and "osteosclerosis" in which osseous structure increases in density. Almost all conditions capable of producing sclerosis may also produce some degree of hyperostosis. On the other hand, hyperostotic lesions may be of decreased, normal or increased density. Compensatory hyperostosis[178] of all or a portion of the cranium develops secondary to severe underlying brain damage, such as cerebral atrophy, hydrocephalus or porencephaly. This type of hyperostosis, however, is always accompanied by either microcephaly, or asymmetry of the cranium, so that the distinction with other types of hyperostosis is readily made. Racial hyperostosis[147] with a generalized increase in bone density throughout the vault is seen normally in a small proportion of Negroes.

In the differential diagnosis of sclerotic cranial lesions, many occur predominantly in childhood while others occur in adults. Another group of lesions may be seen at any age, and these will be considered first.

About 20% of all patients with fibrous dysplasia have cranio-facial lesions[157]. These may be monostotic, or part of the osseous involvement of polyostotic fibrous dysplasia, or Albright's syndrome in which the polyostotic lesions are accompanied by endocrine mani-

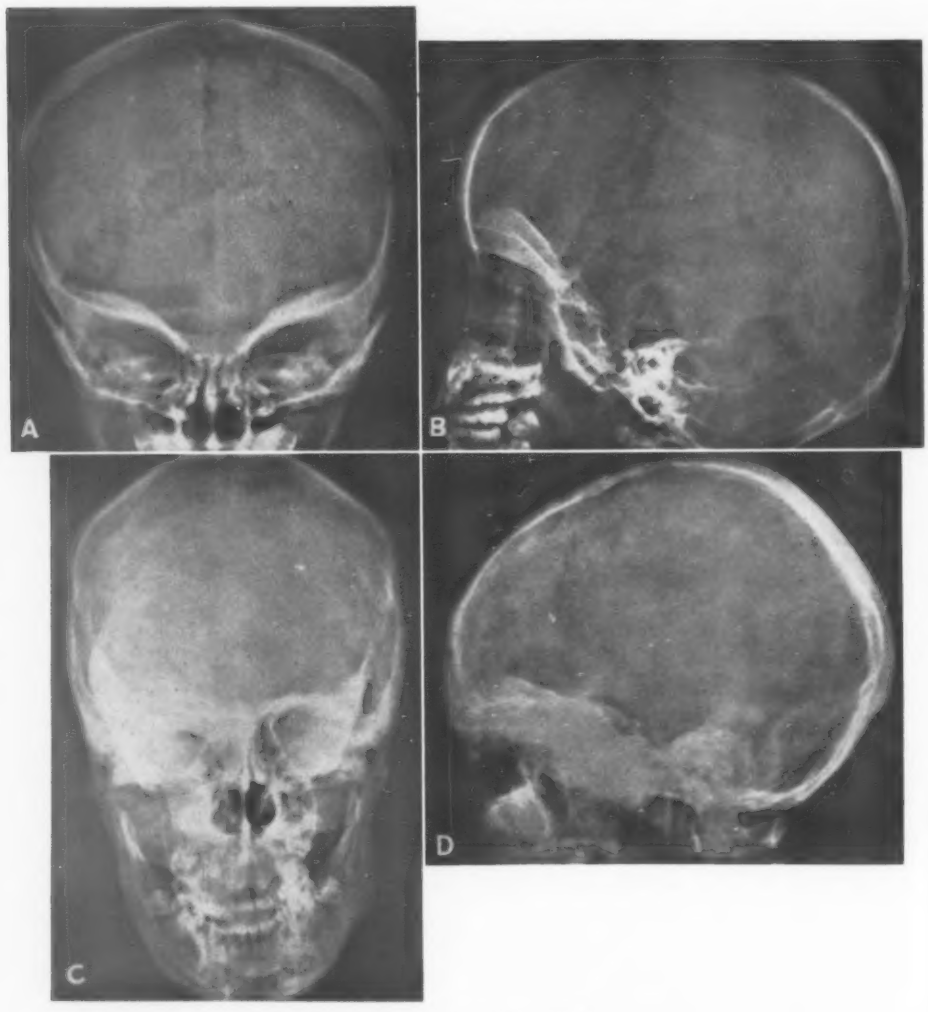
festations. The radiological picture is quite varied, and has been classified into three types: sclerotic, pagetoid and cystic. The most typical appearance is a dense homogeneous asymmetrical sclerosis and hyperostosis of the facial bones and anterior base of the skull[87,191]. Growth over many years may cause marked deformities of the face and orbits, obliterate the sinuses, and encroach on the cranial nerves[63]. The mandible or vault may be involved in the sclerotic process. Lesions in the occipital and temporal areas are relatively unusual, but occasionally the entire cranium is affected. The hyperostosis is sometimes confined sharply to one cranial bone. There are frequently multiple separate areas of involvement with the bone structure between the lesions remaining perfectly normal. This characteristic helps in the differentiation from hyperparathyroidism, because the lesions of the appendicular skeleton in the two diseases may be rather similar. The pagetoid picture of the calvaria presents a combination of areas of sclerosis with areas of rarefaction and distortion of the trabeculation[43]. The external table is often involved more extensively than the inner table and the lesion may project somewhat from the skull surface. Fibrous dysplasia is most commonly seen in young adults, but is often seen in the older age groups also.

Luetic osteitis of the skull is frequently a dense homogeneous hyperostosis of the anterior base of the skull, facial bones and mandible. The hyperostosis may, however, involve a portion or the entire calvaria. There may be alternating areas of destruction and sclerosis. Parrot's node, a localized bony projection from the external table of the skull in congenital lues is now rarely encountered. Tuberculosis rarely causes proliferative osteosclerosis of the basal skull and facial bones, simulating luetic osteitis[120].

Among the various neuro-cutaneous syndromes, tuberous sclerosis most commonly produces changes in the cranium. Multiple small plaque-like zones of sclerosis of the inner table and diploe immediately overlying the firm tuberous nodules at the surface of the hemispheres produce a distinctive radiological appearance[47,48]. These lesions are present in 40% of all cases[90]. They are frequently so small and faint however, that they may be easily mistaken for intracranial calcifications. The islands of increased density appear at puberty and are not seen in young children. In Sturge-Weber angiomatosis hyperostosis of a portion of the calvaria is occasionally seen, either overlying an area of cerebral atrophy, or underlying an extensive area of cutaneous angiomatosis. In neurofibromatosis, areas of sclerosis and hyperostosis of the calvaria or base are rarely seen[63].

Several types of osteochondrodysplasia may cause sclerosis and hyperostosis of the skull beginning in childhood and extending into adulthood. The commonest finding is a symmetrical sclerosis of the base. In osteopetrosis (marble bone disease) the earliest change is sclerosis of the sphenoid with obliteration of the sphenoid sinus. The process then extends along the base of the skull to involve the maxillary and nasal bones. The entire calvaria is sometimes involved, but the mandible is frequently spared[63]. In a few instances in the literature, patches of rarefaction in the parietal bones have been present, in addition to the sclerotic changes[63]. The entity "cranio-metaphyseal dysplasia"[96], has long bone abnormalities identical with Pyle's disease (familial metaphyseal dysplasia)[128,131], and sclerosis of the base of the skull. The dorsum sellae is often thickened. The

sinuses and foramina of the base of the skull may be encroached upon and the pneumatization of the mastoids obliterated. There may be narrowing of the base of the skull from side to side[65]. About two-thirds of all patients with Engelmann's disease (progressive diaphyseal dysplasia[80,132,182], have a progressive sclerosis of the anterior base of the skull. The calvaria may also be involved, with sclerosis particularly of the inner table. The changes are sometimes asymmetrical. Rarely, only a single bone such as the temporal or sphenoid may be involved[171]. In rare instances of osteogenesis imperfecta[63], sclerosis has been present in the base, and frontal and parietal portions of the vault. Only a few instances of melorheostosis involving the skull are known in the literature[71,89], tending to involve only one side of the cranium including



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the mandible; the condition is sometimes associated with scleroderma[89]. There is sometimes mild sclerosis of the anterior base of the skull in Hurler's syndrome. The multiple small dense foci typical of osteopoikilosis have been described in the skull apparently in only one reported case[159]. A variety of skeletal dysplasias with areas of sclerosis in the skull have been reported in the literature which have not conformed to any of the recognized entities[129].

SCLEROTIC CRANIAL LESIONS OCCURRING PREDOMINANTLY IN CHILDHOOD. Any prolonged hematological disturbance

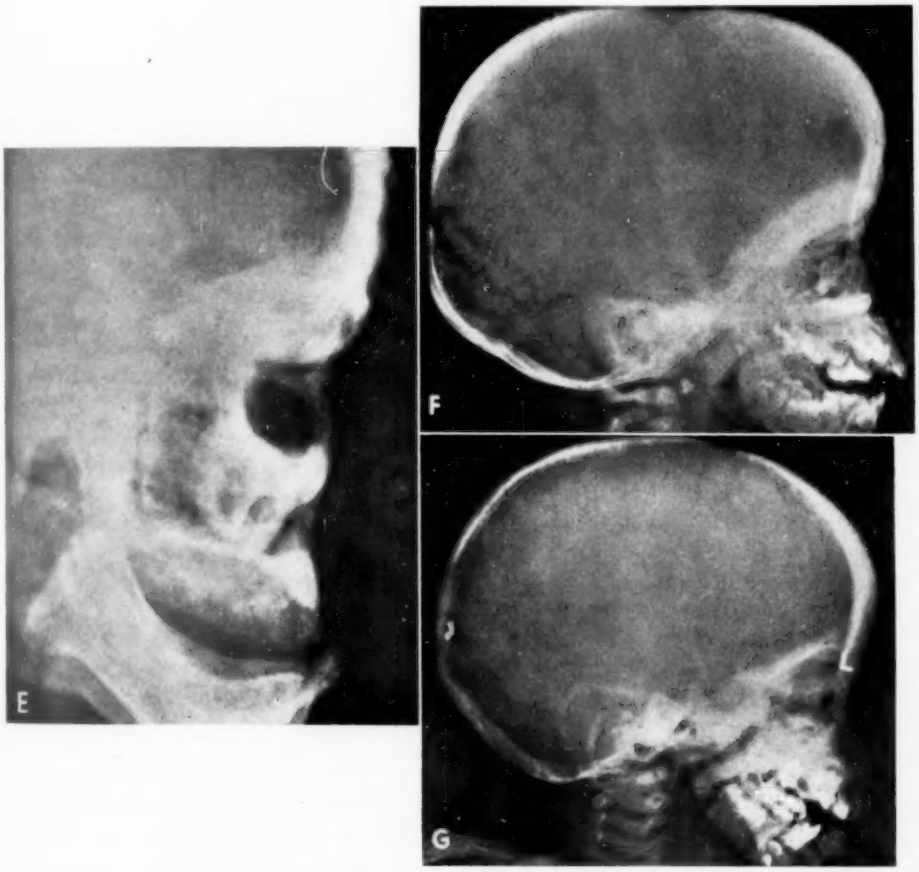

Fig. 3.—Sclerotic cranial lesions.

(*A*) and (*B*) Severe cyanotic congenital heart disease with bone marrow hyperplasia producing symmetrical sclerosis of frontal and sphenoid portions of the base of the skull. Numerous wormian bones along the lambdoid suture.

(*C*) and (*D*) Craniofacial fibrous dysplasia in Albright's syndrome, with marked asymmetrical thickening and sclerosis of anterior base.

(*E*) Luetic osteitis producing sclerosis of facial bones and anterior base, and complete destruction of nasal bones.

(*F*) Congenital hemolytic anemia. Sclerosis more marked in anterior base. Sclerosis of frontal and parietal vault accompanied by spiculation.

(*G*) Renal osteodystrophy with pure sclerosis of the base and "woolly" pattern of sclerosis and rarefaction of the calvaria.

accompanied by hyperplasia of the bone marrow may give rise to a symmetrical hyperostosis and sclerosis of the skull during early childhood. Cooley's erythroblastic anemia (thalassemia major), sickle cell anemia or congenital hemolytic anemia may give rise to similar changes; they are, however, less common with sickle cell anemia, and much less common with congenital hemolytic anemia. Extreme degrees of bony overgrowth are found in a minority of Cooley's anemia patients, and rarely with sickle cell anemia. In Cooley's anemia, there is usually hyperostosis of the frontal and parietal portions of the calvaria, of the anterior base of the skull, particularly the frontal plates forming the floor of the anterior cranial fossa, and sphenoid. Overgrowth of the maxilla with secondary malocclusion of the teeth is fairly frequent. There is usually absent or poor pneumatization of the mastoids and sinuses[18]. The skull changes of Cooley's anemia tend to persist into adult life, whereas the long bone changes tend to regress. Most of the increased thickness of the vault is due to an increase in the diploic layer rather than the tables. In instances where the degree of hyperostosis is less marked, the bony changes may be limited to the anterior base of the skull. Sometimes, the changes involve only the frontal or parietal portions of the calvaria. In sickle cell anemia[25] the distribution of the hyperostosis is quite similar to that of Cooley's anemia; however, the thickening may involve the tables more than the diploic layer[58]. It is frequently best seen in the parietal bone[116]. The increased thickness tends to become less marked as the children become older, and disappears in adulthood[83].

The secondary polycythemia of severe cyanotic congenital heart disease in young children may produce hyperostosis and sclerosis of the skull very similar to that of Cooley's anemia and sickle cell anemia. The mechanism of production of the changes is probably also similar; that is, secondary to prolonged hyperplasia of the bone marrow. Ten children with various cyanotic congenital cardiac conditions accompanied by hyperostotic lesions of the skull have been observed at The Johns Hopkins Hospital. The sclerosis has always been symmetrical, involving predominantly the anterior bases of the skull (frontal plates and sphenoid) and sometimes the parietal portion of the calvaria. There is sometimes marked accentuation of the vascular markings of the calvaria; these have sometimes regressed following cardiac surgery. There may be numerous Wormian bones in the lambdoid suture, indicating retardation of ossification of the vault. In one instance, necropsy revealed marked generalized hyperplasia of the bone marrow. The structure of the hyperostotic bone of the skull appeared relatively normal. Although this is a common cause of cranial hyperostosis in young children, it has not been mentioned in the literature, to the author's knowledge. It is apparently a well known finding however, among pediatric radiologists.

In the healing phases of prolonged rickets, there is frequently marked hyperostosis of the frontal and parietal bones. There may be no increase in bone density. However, in unusual cases, the hyperostosis involves the entire calvaria with a dense structureless appearance simulating that of congenital lues. Usually, the outer table is thickened more than the inner table.

A small proportion of children with renal osteodystrophy have purely sclerotic lesions of the skull with a complete absence of rarefaction. This also rarely occurs in adults. The thickening usually involves the frontal portion of the cal-

varia and the frontal and sphenoid portions of the base[32,44]. Less frequently, purely hyperostotic lesions may be present in the long bones and spine in addition to the skull[200]. The purely sclerotic lesions tend to occur when the condition is of long duration[77].

In the severe form of idiopathic hypercalcemia of infancy, increased density of the base and calvaria is often present[41,114,172]. Rarely a granular or speckled appearance of the calvaria resembling hyperparathyroidism is observed. Sclerosis of the frontal bones, especially of the basal portions, in hypervitaminosis D, is quite rare[72].

Caffey's infantile cortical hyperostosis almost invariably involves the mandible. The disease begins between 3 and 5 months of age. In only 3% of cases[170] is the cranium involved, with sclerosis of the frontal calvaria and anterior base. Scattered patches of sclerosis and decalcification throughout the calvaria are rarely seen[168]. Although the condition usually regresses spontaneously, from 2 to 2½ years are often required for radiological regression.

Mild diffuse hyperostosis of the calvaria is often present in hypoparathyroidism; the bone may be of normal, increased or rarely, decreased density[1]. Similar findings are seen in familial pseudohypoparathyroidism[6,40], due to decreased sensitivity to parathormone. In other members of the family of patients with this abnormality, the skeletal changes may be present without the tetany or hypocalcemia, the so-called "pseudo-pseudohypoparathy-

Schüller-Christian's reticuloendothelroidism."

iosis in the active phase produces only destructive lesions in the skull. However, in the healing phase of destructive areas of the orbit and anterior base of the skull, an asymmetrical sclerosis and thickening are frequently seen[5]. Sclerotic lesions of the calvaria are quite rare.

Approximately half of the fully developed cases of dystrophia myotonia[28,98] have a progressive sclerosis of the anterior base of the skull, frequently affecting the parietal bones as well. There may be progressive thickening of the entire vault[196]. The sinuses are often extensively pneumatized. In young children, the sclerosis may resemble the picture of hyperostosis frontalis interna.

SCLEROTIC CRANIAL LESIONS OCCURRING PREDOMINANTLY IN ADULTS. Hyperostosis frontalis interna, the commonest cause of craniosclerosis in adults is probably best considered as merely a normal variation. It is found in about 12% of all females over 38 years of age, whether symptomatic or asymptomatic. Despite numerous attempts to associate this finding with endocrine abnormalities, no real clinical entity associated with it probably exists[158]. The sclerosis and hyperostosis usually involves the inner table in the frontal region, but also frequently in the parietal area. It is always bilateral, but not always perfectly symmetrical. Some of the lesions may be nodular in appearance. The entire thickness of the calvaria may be involved.

About one-third of all cases of Paget's disease have skull involvement[159]. Any portion or all portions of the cranium may be affected. Lesions of the maxilla are also rather frequent. The thickening of the vault usually involves all three of its layers, especially the outer table. The "woolly" stage of the disease with irregular areas of increased density and radiolucency may slowly become more sclerotic. The completely eburnated calvaria with the complete disappearance of the diploe probably requires at least 15 years to

develop[159]. Even cases with extensive lesions may have normal areas with sharp lines of demarcation from the diseased bone, thereby differentiating from hyperparathyroidism.

The sclerosis and thickening of the frontal plates of the floor of the anterior cranial fossa seen in hyperparathyroidism is almost invariably accompanied by mottled rarefaction of the calvaria[52].

Localized, asymmetric, single or multiple patches of sclerosis and hyperostosis may be due to osteoblastic metastases from carcinomas of the prostate or breast. The lesions frequently involve the middle cranial fossa, and may encroach on the optic and other foramina. The hyperostosis may be so marked as to simulate meningioma or fibrous dysplasia[156].

Osteomyelosclerosis (due to myeloid metaplasia) has involved the cranium only in rare instances[136]. Radiologically similar lesions of the spine and proximal extremities have been observed in urticaria pigmentosa. Whereas in most cases of this condition the skull is not involved[180], sclerosis has been observed in the base. Sometimes islands of condensation develop in the calvaria which later coalesce to form large sclerotic areas[160].

Chronic radium poisoning, after a latent interval of many years, may produce sclerosis of the base of the skull, especially of the middle fossa[117], accompanying the widespread eburnation throughout the skeleton. The widespread sclerosis of the skeleton encountered in fluorosis often involves the mandible. The other facial bones, base of skull or calvaria may be affected. In a few cases of long duration, extreme degrees of hyperostosis and sclerosis of the entire cranium have been seen[67].

Acromegalics frequently have hyperostosis of the calvaria, particularly at the vertex, inion, and supra-orbital ridges. The zygomatic arches are thickened. The paranasal sinuses, especially the frontal, are over-developed[127].

RADIATING SPICULES OF THE CALVARIA. This radiological sign is also referred to as "sun-burst," "hair-on-end," or "tooth-comb" appearance. Multiple thin parallel radiolucent lines are seen in a hyperostotic calvaria running perpendicular to the tables. The lines usually run from the inner to the outer table. While this sign has been called characteristic of certain diseases in the past, it is actually nonspecific[81]. It is usually observed in the parietal areas on either side, but may extend into the frontal region when the hyperostosis is marked. It has been referred to as the "brush skull" or Burstenshadel of Cooley's erythroblastic anemia. It has been observed in only $2\%^{190}$ to $8\%^{25,116}$ of children with sickle cell anemia. It is even more unusual in congenital hemolytic icterus[34]. The lesion has also been observed in meningiomas[21], metastatic osteoblastic carcinoma of the thyroid[21], hemangiomas of the vault[15,151], and luetic osteitis. A minimal degree of spiculation may be seen occasionally in normal subjects.

This sign is quite commonly seen in neuroblastoma and sometimes in leukemias[192] in childhood; the spicules may project beyond the outer table and be accompanied by overlying soft tissue swelling.

SMALL SELLA TURCICA. Many normal individuals have a pituitary fossa quite small in size. In non-neoplastic hypopituitarism, the pituitary fossa is not significantly reduced in size below the ranges of normal. Sclerotic and hyperstotic lesions of the base of the skull however, may markedly decrease or completely obliterate the fossa. This finding is usually present in dystrophia myotonia[28,196]. It is occasionally seen in fibrous dysplasia, osteogenesis im-

perfecta, osteopetrosis, cleidocranial dysostosis, cranio-metaphyseal dysplasia[65], and Werner's syndrome[142]. It is uncommon in achondroplastic dwarfs.

LEONTIASIS OSSEA. The term "leontiasis ossea" has been defined in so many different ways in the medical literature that its use has been condemned[163]. It has been used synonymously with hyperostosis of the cranium[139] and synonymously with fibrous dysplasia of the facial bones[63]. It is commonly regarded not as a pathological entity, but descriptive of a clinical syndrome[174]. An insidious progression of facial deformity due to massive thickening of the underlying facial bones, usually begins in childhood or adolescence. Encroachment eventually occurs on the orbits, nasal cavities, sinuses and optic foramina, resulting in exophthalmos, hypertelorism, cranial nerve damage and malocclusion. Sixty per cent occur in males, and two-thirds have bilateral involvement[141].

The commonest cause of the syndrome is fibrous dysplasia, either monostotic or polyostotic. It is rarely familial[163]. The monostotic form has been reported with polyposis of the colon[141]. The second commonest cause is Paget's disease of bone. About one-third of the cases of osteopetrosis have some degree of facial deformity[62]. The syndrome has also been observed in hyperparathyroidism secondary to renal disease[39], pituitary giantism, syphilic osteoperiostitis, cranial metaphyseal dysplasia, Engelmann's disease, and multicystic lesions of the jaws, including cherubism.

Pathological Intracranial Calcifications. VASCULAR CALCIFICATION. The commonest pathological calcification is that of the internal carotid artery, lying in the para-sellar region on either side. This is seen in 2% of all skull films, in 4% between the ages of 50 and 60 years, and in 10% in subjects over 70 years[24]. It appears prematurely in tertiary lues, diabetes, and in metastatic calcification secondary to hypercalcemia. This latter condition occurs in primary hyperparathyroidism, renal osteodystrophy, hypervitaminosis D, Paget's disease, idiopathic hypercalcemia, fluorosis and progeria[142]. Metastatic calcification occurs at other sites, such as the falx, tentorium, the dura, along the superior sagittal sinus, and choroid plexuses of the lateral ventricles. This, however, is of no value diagnostically because it is so commonly seen in normal individuals. Annular metastatic calcifications of the cornea may be demonstrated in special lateral tangential films using soft tissue technique[68].

INTRACEREBRAL CALCIFICATIONS. In asymptomatic individuals, multiple foci of irregular calcifications are sometimes seen, especially in the subcortical tissues, the so-called "idiopathic brain calculi." They are, however, sometimes associated with epilepsy[75].

The ova of certain parasites frequently lodge in the brain substance forming multiple cysts; only a small proportion of these cysts, however, will show radiologically because calcification is a late phenomenon[48]. In cysticercosis, calcifications are visible in only 10%[4,51] to 33%[134,147]. In the brain, these deposits of calcium are usually small, globular, discrete and scattered haphazardly[4,198], contrasting with the much commoner fusiform calcifications in the thigh and other muscles[24]. Minute calcifications may be observed in the eye. Solitary intracerebral calcification is not unusual[147]. Radiologically visible calcium usually takes 5 years to develop after the infestation[51]. Cysticercosis causes increased intracranial pressure in about one-third of all cases with cerebral involvement[4,134,147].

Hydatid cysts of the brain are usually

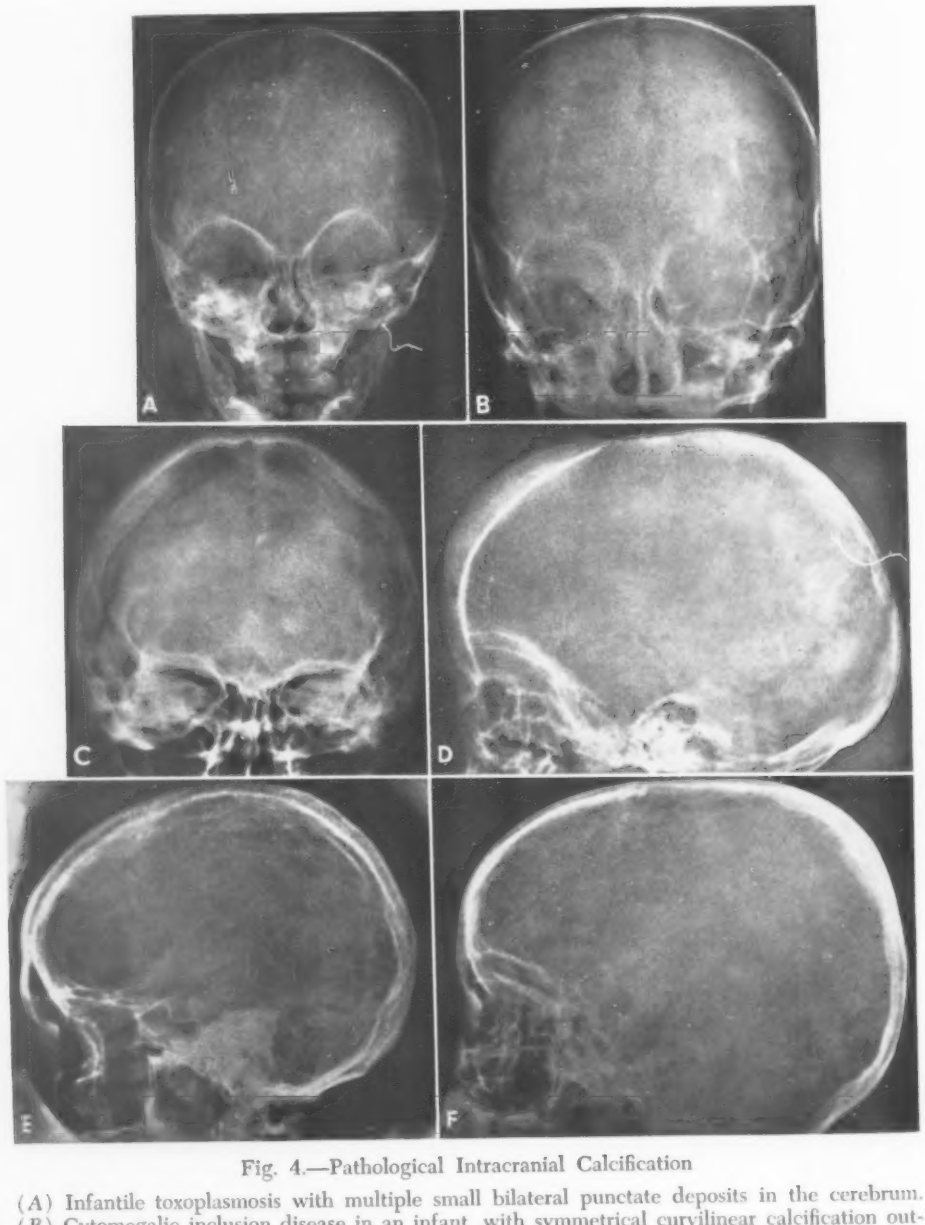

Fig. 4.—Pathological Intracranial Calcification

(*A*) Infantile toxoplasmosis with multiple small bilateral punctate deposits in the cerebrum.
(*B*) Cytomegalic inclusion disease in an infant, with symmetrical curvilinear calcification outlining the dilated lateral ventricles.
(*C*) Symmetrical calcification of basal ganglia due to hypoparathyroidism.
(*D*) Sturge-Weber angiomatosis with marked frontal hyperostosis underlying extensive cutaneous lesions. Faint calcification in posterior parietal and occipital areas; the usual "double contour" distribution of the calcium is not visible.
(*E*) Tuberous sclerosis with a few intracranial calcifications centrally placed. Multiple small foci of sclerosis are seen peripherally, especially in posterior parietal calvaria.
(*F*) Calcified tuberculomas with oval or irregular shape.

rather large[42]. When they are extensively calcified, the ring-like shadows of the partially collapsed cysts enable the correct diagnosis to be made[135]. In many instances, however, the calcification is very incomplete, so that only multiple minute flecks are visible, an appearance similar to many other intracerebral diseases[135]. Hydatid cysts are often found in children[125]. Uncommonly, superficial cysts may cause thinning of the overlying calvaria. Paragonimiasis may cause multiple small cystic calcifications[101].

In the neurocutaneous syndromes, intracerebral calcifications of specific types are quite frequent. The majority of patients with Sturge-Weber cephalotrigeminal angiomatosis (cephalic neurocutaneous hemangiomatosis) have pathognomonic "double contour" calcifications following the distribution of the cerebral sulci[46,109,144]. The calcium becomes deposited in the second and third layers of the cerebral cortex, tending to concentrate in the depths of the cerebral sulci[103]. It is most commonly seen in the occipital lobe, but may be distributed in any part or all of a cerebral hemisphere. While the presence of calcification is the rule in the older age groups, it may be absent in children, and is never present under the age of 18 months[144]. The calcifications may be present in association with mental retardation, but without the cutaneous hemangiomatosis[24]. About half the patients with tuberous sclerosis[7,47,48] have intracerebral calcifications. They are usually small, scattered and discrete (80% of all cases)[185], located in the basal ganglia, para-sellar areas, dentate nuclei, choroid plexuses, or anywhere in the brain[8]. They may be subcortical. Uncommonly, the calcifications may be as large as several centimeters in diameter; rarely, irregular sinuous and single calcifications are seen[185]. The lesions may rarely cause obstructive hydrocephalus. Multiple superficial calcified gliomas have been reported in neurofibromatosis.

Hypopituitarism is quite commonly associated with calcified suprasellar tumors. From 55% to 70% of all craniopharyngiomas are calcified, and about 50% of gliomas of the optic chiasm or hypothalmus are calcified[111]. Uncommonly, pinealomas will show calcification.

INTRACEREBRAL CALCIFICATIONS ENCOUNTERED PRINCIPALLY IN CHILDHOOD. Neonatal cytomegalic inclusion disease, presumably of viral origin, produces fine deposits of calcium in a characteristic paraventricular distribution, usually outlining the contours of the dilated lateral ventricles perfectly[82,122,153]. The lesions are seen only within the first 2 months of life, as the disease is uniformly fatal. There may be numerous calcifications in the basal ganglia or thalami[148,153]. Rarely, the calcifications are unilateral, or curvilinear and then suggestive of toxoplasmosis[148].

In the neonatal form of toxoplasmosis the small inflammatory nodules disseminated throughout the central nervous system become calcified in over 80% of infants[70,184]. Intracranial calcifications are almost always visible several weeks after birth[26]. Most of the lesions are sub-cortical. Deposits in the basal ganglia and thalami[23,54] are also frequently seen, sometimes in streaks or large clumps. Most of the calcifications are seen in the occipito-parietal region. Sometimes only one or two deposits are present. When peripheral calcifications are linear, curvilinear, or comma-shaped, they are characteristic[184]. If the infants survive, the calcified nodules may slowly increase in size during childhood.

Torulosis (cryptococcosis) may cause multiple small discrete calcifications in the newborn similar to toxoplasmosis.

Most of the lesions lie superficially. The head tends to be somewhat larger than normal[133].

Multiple scattered minute calcifications have been reported throughout the brain following epidemic polioencephalitis[24].

Tuberculomas of the brain are becoming progressively rarer in the U.S.A.[194], and only about one tuberculoma in 100 shows calcification radiologically[161]. Slightly over 50% occur in children under the age of 10, and two-thirds occur in males[161]. The densities may be single or multiple, large or small[42,187]. The largest deposits tend to occur in the cerebellum[118]. They usually have a nonspecific appearance, being irregular, angular or serrated, sometimes fragmented, and frequently lying close to the brain surface[24]. Their appearance is often identical with a cerebral hematoma.

About 70% of children with healed tuberculous meningitis[74,112] develop small clusters of fine calcifications along the base of the skull in the basal cisterns, usually appearing 2 to 3 years after the beginning of streptomycin therapy. The common location is just above the sella, corresponding to the site of the densest meningitic exudate. These deposits have no relation to neurological sequelae. The skull films also frequently show calcified cerebral tuberculomas[112]. Meningitic calcification of this type has also been rarely observed with pneumococcal[107] or chronic coccidiodal[149] meningitis.

Rarely, metastases from osteogenic sarcomas may produce intracranial ossification[84].

CALCIFICATION OF THE BASAL GANGLIA. Calcification at this site commonly occurs in a variety of conditions accompanied by deposits elsewhere in the brain[55]. They are observed in encephalitis, tuberous sclerosis and toxoplasmosis. Bilateral and symmetrical calcification localized to the basal ganglia, however, occurs predominantly in hypoparathyroidism[56], pseudohypoparathyroidism[40], or in severe cerebral atrophy dating from birth. In rare instances, unilateral or bilateral basal ganglia calcification has been observed in asymptomatic individuals[69].

In hypoparathyroidism the calcium tends to be deposited chiefly in the anterior portion of the globus pallidus, and frequently has a wavy appearance[24]. The multiple discrete calcifications occasionally coalesce to form a single homogeneous density[56]. The calcium apparently deposits in colloid within and around the fine arterioles. The deposition is apparently related to the high serum phosphorus[56]. Peripheral cerebral calcifications are observed in only rare instances[23].

Microscopic calcifications of the basal ganglia are extremely common as merely part of the generalized aging process[23]. Radiographs of brain specimens from routine necropsies have shown minute calcifications in about 2%, unassociated with any specific disease process. This calcification, however, is much less in degree than that detected *in vivo* in hypoparathyroidism.

Bilateral calcifications of the dentate nuclei are not associated with hypoparathyroidism. Several instances, however, have been observed in Paget's disease[102] and tuberous sclerosis[90].

Changes in the Teeth and Jaws in Systemic Disease. Dental films are invaluable in the study of general affections, because findings in the teeth and mandible are present in a relatively high percentage of cases. Detailed bone structure may be studied under the best possible radiographic conditions throughout the body, with a minimum of overlying soft tissues. The mandibular bone marrow is physiologically quite active. The rarefying diseases of bone are readily demonstrated in the

mandible. The fact that the teeth do not lose density with generalized osteoporosis or osteomalacia makes the decalcified mandible stand out in contrast[176]. Diseases which retard the development or eruption of teeth, particularly the endocrine disturbances, can be dated as to their time of onset.

ALTERATIONS IN DENTITION. A change in the normal times of eruption of the deciduous or permanent teeth may be brought about by a wide variety of chronic diseases. This is often associated with delayed closure of the fontanelles and sutures of the skull, and delayed epiphyseal development in the extremities. The common generalized causes of delayed dentition are as follows: idiopathic or constitutional, cretinism, hypopituitarism, mongolism, severe rickets or renal osteodystrophy, severe idiopathic hypercalcemia, hypogonadism, hypophosphatasia[149], achondroplasia, cleidocranial dysostosis, osteopetrosis, Engelmann's disease, progeria[176], and chondroectodermal dysplasia[19] (Ellis-Van Creveld syndrome). The common causes of accelerated dentition are: constitutional precocity, adrenogenital syndrome, hyperthyroidism from early childhood[176], pseudo-hypoparathyroidism[40], and osteogenesis imperfecta[177].

GENERALIZED RARIFYING LESIONS OF THE JAWS. Any generalized rarefaction of the jaws produces a thinning or disappearance of the lamina dura surrounding each tooth. The continuous radiopaque line which forms the lower boundary of the maxillary sinuses also undergoes these same changes; study of this line is valuable, especially in edentulous jaws where the lamina dura is no longer present. Hyperparathyroidism has sometimes been wrongly considered as the only cause of disappearance of the lamina dura. Whenever the skeleton is involved in this disease, however, dental changes are invariably present[176]. Sometimes cystic areas of radiolucency are visible in the mandible. Following successful removal of a parathyroid adenoma, the lamina dura of the teeth is slowly restored. Other important causes of rarefaction of the jaws are as follows: rickets, especially of the resistant type[140], renal osteodystrophy, Cushing's disease, osteomalacia, idiopathic hypercalcemia[41], osteogenesis imperfecta, oxalosis[53], and Paget's disease in the early phase. In fibrous dysplasia[11], the loss of lamina dura is confined to localized lesions.

Sickle cell anemia and sickle cell hemoglobin-C disease[145,152] are almost always accompanied by areas of radiolucency in the jaws. These are best seen in the mandible below the molars. The few trabeculae remaining between the roots are sharply defined and horizontal, producing a "step-ladder" effect. The lamina dura may seem dense.

DESTRUCTIVE LESIONS OF THE JAWS. In childhood, tuberculous destruction of the jaws has rarely been observed[121]. In about one-third of all cases of Schüller-Christian disease, destructive or multicystic lesions of the jaws are present, usually accompanied by ulcerative lesions of the gums[5]. The erosion first begins in the periapical region[178], extending all around the teeth, so that they appear to "float" in tumor tissue[88]. Later the teeth become displaced and exfoliated[5].

Cystic destruction of the jaws may occur with fibrous dysplasia[167], oxalosis[53], or neurofibromatosis[63].

Many different types of malignancy may metastasize to the jaws, especially to the mandible[27], as follows: carcinomas of the breast, kidney, thyroid, lung and prostate, sarcomas of the ovary, breast and bone, lymphomas, malignant melanoma, and myeloma. Rarely the initial lesion of myeloma may be an osteolytic area in the mandible[119]. Myelomatous destruction often

begins around the mandibular canal extending into edentulous areas. Sometimes it has a multicystic appearance[178].

GENERALIZED LESIONS CAUSING SCLEROSIS OF THE JAWS. Sclerosis of the jaws is readily detected by the coarsening and distortion of the trabecular pattern. In Caffey's infantile cortical hyperostosis the mandible is almost invariably involved[168] with subperiosteal new bone formation. Sclerosis is also seen in infants with idiopathic hypercalcemia[41]. All degrees of sclerosis are encountered in fibrous dysplasia[11], sometimes with gross alterations in architecture. The sclerosis of Paget's disease is usually accompanied by hypercementosis of the roots of the teeth[176]. In a few cases of sickle cell anemia or sickle cell hemoglobin-C disease, localized areas of osteosclerosis corresponding to areas of infarction are seen[145]. Conditions causing complete eburnation of the mandible, such as osteopetrosis, fluorosis[67,181] and radium osteitis[117] predispose to erosion of the enamel and dentin, to periapical infections and osteomyelitis.

WIDENING OF THE PERIODONTAL MEMBRANE. Widening of the periodontal membrane of the entire roots of the posterior teeth due to an increase in collagen is a characteristic finding of scleroderma[179]. The sign, however, is present in only about 7% of cases.

DEVELOPMENTAL DEFORMITIES OF THE TEETH. Only diseases occurring early in life may effect the development of the teeth, because their formation is relatively complete at 2 years. The Hutchinson's teeth of congenital lues have a notched incisal edge of the central incisors and "screw-driver shaped" crowns[178]. Hyperplasia of the enamel and malocclusion may occur in infantile rickets[178]. A persistence of deciduous teeth and absence of the incisors has been noted in congenital hemolytic anemia[174]. In hyperpituitarism there may be enlargement of the roots[177] while in hypopituitarism dating from early infancy, the jaws are slightly underdeveloped and the teeth slightly crowded[176]. When the onset of hypoparathyroidism occurs younger than the age of 3 years, hypoplasia of the enamel and dentin occurs, as evidenced by underdeveloped and short roots. These findings may occur from any prolonged hypocalcemia in early life. A prolonged retention of primary teeth with over-crowding of the permanent teeth is seen in progeria.

Partial or complete aplasia of the teeth is common in anhydrotic ectodermal dysplasia with hypotrichosis and atrophic rhinitis. Teeth which do develop are usually diminutive[177]. The front teeth may be peg-shaped and widely separated[188]. Hypoplastic, irregular or cone-shaped teeth widely separated may also occur with chondroectodermal dysplasia[19].

There is a profound disturbance in dental development in cleidocranial dysostosis with faulty implantation, over-crowding, impactions and malocclusions, defective enamel and roots, supernumerary buds and dentigerous cysts[139]. A specific dental abnormality "dentinogenesis imperfecta" or hereditary opalescent dentin" occurs in osteogenesis imperfecta. The roots are poorly formed with calcification only at the periphery, and an absence of pulp chambers and root canals. Partial anodontia or cone-shaped crowns of the maxillary incisors are rarely seen in achondroplastic dwarfs; there is occasionally crowding of the teeth superficially simulating cleidocranial dysostosis.

PROGNATHISM. Protrusion of the mandible is caused classically by acromegaly or pituitary giantism[176], but is also occasionally seen with cleidocranial dysostosis, cretinism, Hurler's syndrome, and dystrophia myotonia[29].

RODENT FACIES. An apparent underdevelopment of the mandible may be due merely to an overgrowth of the maxilla (leontiasis ossea). It may occur in cleidocranial dysostosis, or localized mandibulo-facial dysostosis. Underdevelopment of the mandible has occurred in rheumatoid arthritis of early childhood, due to permanent damage of the temporomandibular joints[59].

Conclusion. There are still some obvious gaps in the knowledge of the effects of the systemic diseases on the skull, especially in the diseases of childhood. The incidence of many of the radiological signs of the generalized diseases in the skull is not known. The full potential of skull Roentgen-ray films, particularly dental studies has not yet been realized, as an aid in differential diagnosis.

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BOOK REVIEWS AND NOTICES

ENDOCRINE ASPECTS OF BREAST CANCER. Edited by ALASTAIR R. CURRIE, B.Sc., M.B., F.R.C.P., University of Glasgow. Pp. 339; 104 ills. Edinburgh and London: E. and S. Livingstone, Ltd., 1958 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $8.50.

THIS volume contains the proceedings of a conference held in July, 1957, under the auspices of the University of Glasgow. The papers presented are generally excellent and represent the results of both basic and clinical investigations. It is clear that, in many instances, breast cancer can be favorably altered by hormonal therapy or endocrine ablative procedures. Some of the more important problems that remain to be completely solved are: (1) the mechanism by which changes in the hormonal environment alter tumor growth (2) the determination of hormone dependency of tumors and (3) the selection of the method of therapy in individual cases that will afford the best chance of response.

Today the physician is in a position to offer many patients with metastatic breast cancer a significant number of months or even years of comfortable remission. Only by a thorough understanding of the hormonal relationships and the alterations brought about by the various therapeutic procedures can one hope to outline a rational plan of therapy. This volume is the most complete work to date on the subject. B. C.

THE FUNCTIONAL ORGANIZATION OF THE DIENCEPHALON. BY W. R. HESS, Professor of Physiology, Emeritus, University of Zurich, Zurich, Switzerland. Edited by JOHN R. HUGHES, M.A. (OXON) PH.D., National Institute of Health, Bethesda, Maryland. Pp. 180; 82 ills. New York: Grune & Stratton, Inc., 1957. Price, $7.00.

THIS translation of "Das Zwischenkirn" represents an English summarization of W. R. Hess's important contributions to Neurophysiology. For this work and other contributions, Professor Hess was awarded the Nobel prize in 1949.

Part I deals with the hypothalmus and vegetative (autonomic) functions. Part II presents extrapyramidal motor functions of the diencephalon and Part III is devoted to data on methods and instructions on experimental techniques.

This work is profusely illustrated with pertinent photographs of the animals during and after the experiments. There are also numerous plates which clearly show the neuroanatomical location of the lesions.

Dr. Hess was a pioneer in this field and a knowledge of his work is indispensable to the neurophysiologist, neurologist, or neurosurgeon working in this field. M. S.

THE STRESS OF LIFE. BY HANS SELYE, M.D. Pp. 324; illustrated. New York: McGraw-Hill Book Co., Inc., 1956. Price, $5.95.

THE author's concept of stress and its interrelation with a wide variety of diseases of man are well known to physicians and many others of the scientific community. It is unnecessary, therefore, for the reviewer to restate those views here. In this book, however, Dr. Selye has undertaken an explanation of his theory of stress for the general reader. This he has accomplished in a readable and lucid style. Indeed, members of the profession may also find this book to be both interesting and thought-provoking. C. Z.

ANOMALÍAS MORFOLÓGICAS DE LA PLACENTA Y SU SIGNIFICADO CLÍNICO. BY DR. OSCAR AGÜERO, Professor of Clinical Obstetrics, Central University of Venezuela; Attending obstetrician of the Maternity "Concepcion Palacios;" Director of the Journal of Obstetrics and Gynecology, Venezuela. Pp. 107; 27 ills. Caracas, Venezuela: Artegrafia, C. A., 1957.

DR. AGÜERO presents an anatomically and clinically complete description of the anomalies of the placenta, expressing his opinion based on 10,000 personal placental examinations. He stresses careful placental examinations to prevent overlooking anomalies which may be causes of complications otherwise unsuspected. The analysis of circumvallata placenta is excellent; his incidence of complications associated with this anomaly is lower than those reported elsewhere. He denies an increase in fetal deaths with this anomaly.

The monograph is profusely illustrated with

excellent black and white photographs and line drawings of variations in placental structure. J. M.

DIAGNOSTIC MEDICAL PARASITOLOGY. By EDWARD K. MARKELL, PH.D., M.D., AND MARIETTA VOGE, M.A., PH.D., Division of Parasitology and Tropic Diseases, Department of Infectious Diseases, School of Medicine, University of California, Los Angeles. Pp. 266; 115 ills., 5 in color. Philadelphia: W. B. Saunders Company, 1958. Price, $7.00.

As the authors point out in the introduction, this text definitely serves as an excellent guide to both the laboratory and clinical diagnosis of protozoan and helminthic diseases of medical importance.

Unlike most textbooks in parasitology the parasitic infectious agents are considered in relation to the various organ systems affected, that is, Intestinal Parasites, Blood Parasites, Parasites of the Genito-urinary System and the Tissue Parasites. Also included in the text are chapters concerned with Arthropods and Human Diseases, Host-Parasite Relationships, Procedures in Examination of Stool Specimens, Procedures in Examination of Blood Parasites, Pseudoparasites and Pitfalls, Special Diagnostic Methods and a chapter on Fixatives, Stains and Common Procedures. This approach to the science of parasitology is noteworthy since the emphasis in most medical schools is on correlative teaching.

The book is well illustrated with line drawings, sketches and photographs.

Although the text was primarily designed for the teaching of parasitology to medical students, the book should find excellent usage for the medical technologist and other personnel whose main interest is concerned in the laboratory diagnosis of parasitic diseases.

In spite of its size the authors have succeeded in covering an exceedingly large amount of pertinent clinical and biologic material. E. G.
A. L.

PROCEEDINGS OF THE SIXTH INTERNATIONAL CONGRESS OF THE INTERNATIONAL SOCIETY OF HEMATOLOGY, Boston, August 27–September 1, 1956. Edited by PUBLICATIONS COMMITTEE, A. RICHARDSON JONES, M.D., CHAIRMAN. Pp. 930; illustrated. New York: Grune & Stratton, Inc., 1958. Price, $25.00.

THIS volume represents the accumulated contributions of participants in the Sixth International Congress of Hematology which was held in Boston in 1956. The material is grouped under 7 major headings: 1) Leukemia; 2) Nucleonics; 3) Spleen and Hypersplenism; 4) Hemorrhagic Disorders; 5) Anemia; 6) Immunohematology; and 7) Miscellaneous.

Although many of the papers are published in complete text, many more are recorded in abstract form only. Despite this lack of completeness, hematologists and others will find much in this volume that is new and interesting. C. Z.

THE RELATION OF PSYCHIATRY TO PHARMACOLOGY. By ABRAHAM WIKLER, M.D. Pp. 322. Baltimore: The Williams & Wilkins Co., 1957. Price, $4.00.

THIS timely volume comprehensively reviews the literature dealing with the chemotherapy of functional psychoses and psychoneuroses. Some 889 references which appeared during the period 1930 to 1955 have been "scanned" for pertinent information in this broad and difficult area. The material is presented in two major sections. The first has to do with the effects of drugs on human behavior, and has subsections on therapeutic procedures, testing procedures for diagnosis and prognosis, and on the production of "model" psychoses. In the second section the theories and mechanisms of drug actions are considered. Subdivisions take up biochemical, neurophysiological, and psychological aspects of respective compounds.

The author is to be congratulated for the preparation of this splendid summary. All who are concerned with neuropsychiatric problems, from both the clinical and research standpoints, will find this review an invaluable aid. C. Z.

YEAR BOOK OF DRUG THERAPY (1957–1958 SERIES). Edited by HARRY BECKMAN, M.D., Pp. 518; 44 ills. Chicago: The Year Book Publishers, Inc., 1958. Price, $7.50.

LIKE its predecessors in this series, abstracts of articles dealing with a wide range of therapeutic agents comprise this volume. Both specific and symptomatic forms of treatment are included. Thus, sections are devoted to developments in the management of allergic, cardiovascular, gastroenterologic, hematologic, renal, hepatic, neuropsychiatric, and infectious disorders. In addition, special attention is given to corticotropin and cortisone, tranquilizers and stimulants, and the relief of

pain and fever, as well as therapy for other important disease problems.

Clinicians will find this well-edited volume a concise and valuable survey of the recent literature on drug therapy. C. Z.

ALDOSTERONE. Edited by ALEX F. MULLER, M.D., AND CECILIA M. O'CONNOR, B.Sc. Pp. 232; 84 ills. Boston: Little, Brown & Co., 1958. Price, $8.00.

THE papers which were presented at an International Symposium on Aldosterone, held in Geneva, Switzerland, in June, 1957, comprise this volume. Included are discussions of the urinary excretion of aldosterone; studies of the functional zonation of the adrenal cortex and of the production of aldosterone; the metabolism of aldosterone in man; primary aldosteronism; edema and aldosterone; and interrelationships of potassium deficiency and renal disease.

Endocrinologists and other clinicians will find much new basic and clinical information in the proceedings of this symposium.

C. Z.

THERAPEUTIC HEAT. Edited by SIDNEY LICHT, M.D., Assistant Professor of Medicine (Physical Medicine), Yale University School of Medicine, New Haven, Connecticut; in collaboration with twenty-two contributors. Pp. 466; 127 ills. New Haven: Elizabeth Licht, 1958. Price, $12.00.

"THERAPEUTIC HEAT" is the title of the second volume of the series called PHYSICAL MEDICINE LIBRARY, edited by the able, versatile physiatrist, Dr. Sidney Licht. This book should exceed in popularity the well-received first volume. The latter dealt with Electrodiagnosis and Electromyography, interest in which is limited to a few specialties. Heat as a form of treatment, on the other hand, is one of the oldest and most widely employed physical procedures in medicine. In spite of this, many well-informed physicians lack understanding of the physiological effects of heat and the indications for its proper use as a therapeutic measure. Therefore, the publication of this new work is timely.

The purpose of this book, as stated in the preface by the Editor "is to shorten the gap between the known facts about heat and its clinical application." How well this has been accomplished will be apparent to the thoughtful reader.

The subject matter is considered in twenty chapters and an appendix on the often overlooked subject of the medico-legal aspects of physical medicine. A satisfactory index and a useful alphabetical list of the authors cited in the text follow. Each chapter is a well-written essay, complete in itself; contributed by recognized authorities on the subjects discussed.

In the first five sections, the basic sciences which are the foundation of physical medicine are thoroughly discussed. In this category the subjects presented are: Physics of Heat, Thermometry, Bio-Physics of Diathermy, Physiology of Heat and Cold, and Thermal Radiation, Pain and Injury. Doubtless, there are those who will be critical of devoting so much space to pure science in a text primarily intended for clinicians. However, physicians and others intent upon establishing a sound scientific basis for the practice of physical medicine, will welcome the informative discussions of the above mentioned topics.

The sections dealing with methods and the clinical application of heat are preceded by an interesting chapter on the history of therapeutic heat, prepared by the Editor. The contributors who have discussed the clinical uses of heat have wisely avoided the all too common practice of advocating the employment of various forms of heat and types of apparatus in the management of specific conditions. They have been content to present authoritative scientific facts and controlled observations based upon extensive clinical experience, leaving the choice of procedures to the individual judgment of the reader.

The last half dozen chapters deal with the indications for the use of heat in the treatment of chronic rheumatic diseases, orthopedics, vascular disorders, neuromuscular conditions, pelvic diseases and diseases of the eye.

In this single volume are included all the important and well-recognized medical uses of heat, discussed from the scientific as well as the clinical viewpoint.

This book is recommended to physicians in general, as well as to the men and women whose primary interest lies in investigation, teaching and practice in the field of physical medicine. G. P.

THE MEDICAL WORLD OF THE EIGHTEENTH CENTURY. By LESTER S. KING, M.D., Clinical Professor of Pathology, University of Illinois College of Medicine, Director of Laboratories, Illinois Masonic Hospital. Pp. 346;

10 ills. Chicago: The University of Chicago Press, 1958. Price, $5.75.

Various avenues are open to the medical reader entering the complex field of medical history. The one usually followed is the chronological approach, whether with emphasis on persons, countries, achievements, specialties, or with a mixture, or rather hodge podge of all, thereby hoping to maintain some degree of balance between the numerous subdivisions. In larger works, requiring space for much detail, the many subdivisions are not easily linked together, and yet with the tremendous expansion of biological knowledge in the last 500 years, a chapter is soon required for each century. Thus we find ourselves in the artificial situation described by Dr. Veith in the Foreword, of being prone to regard a century as a rigid historical unit with all the attendant road blocks that that entails. This difficulty, however, has not hampered Dr. King, who, when necessary, lightly follows his line into the 17th and 19th centuries and even further afield. He develops much of interest in the pursuit of the various social, economic, scientific, intellectual, moral, research, and clinical aspects of the period in a series of sketches which merge finally into a panorama of a cohesive unit. This surprised the reviewer, who had accepted Garrison's view of the 18th century as one of tedious philosophizing and theorizing, as opposed to the evaluations by Baas as a century of enlightenment and by Pagel as one of emancipation from religious and political domination. Among its valuable achievements are noted the wider recognition and, therefore, the increased usefulness of the important discoveries of earlier centuries. No less important was the establishment of scientific institutions, societies and new university departments which facilitated further progress.

The ten chapters—really loosely connected separate essays—are grouped around the Apothecary and Physician and their rivalries, the Quack and the Empiric, Boerhaave as Systematist and Scientist, Fevers, Homeopathy, the Classification of Disease, Medical Ethics, The Rise of Modern Pathology, The Practice of Medicine. In the opening chapter, one not only learns the basis for the complications of English medical degrees and licensing, which with British regard for tradition have not changed since the time of Henry VIII, but also observes how the paths toward a better medical education and the opportunity for legitimate practice were opened up during a short half century. Those who chafe at the time now taken to acquire a medical education may find solace in the fourteen years attendance at Oxford required in earlier days to receive a Doctor of Medicine.

Returning to the 18th century, we learn that the treatment of the sick was divided between the "quack" (or mountebank) and the empiric and the rationalist—each having a different and often overlapping meaning from that understood in classical and in modern times. When John Wesley and Bishop Berkeley of Tar Water fame are contrasted, one is taught the need for knowing these differences in the meaning of terms—a necessity applicable to most all definitions—before passing judgment on a man or his times.

What at first seems like a departure from the author's plan of viewing situations from various aspects is seen in the lengthy analysis of Boerhaave as a Systematist and Scientist, but this is only apparent because of the versatile activities of this great character. He received the most detailed treatment of any individual, both as a systematist (where his logically constructed doctrines so frequently came to grief on the factual rocks of the early 19th Century) and as a scientist (where again he failed in spite of some excellent scientific qualities to make the lasting contribution to medical progress of which he was capable). He was inquisitive, devised experiments from which he derived useful correlations, was hungry for evidence (he knew the value of an autopsy!), sought causes, and critically evaluated conclusions. He used Bacon's reasoning by induction and deduction as if he had read the *Novum Organum* of the previous century, but, in spite of all was often betrayed by his erroneous first principles. The tragedy of Boerhaave, as Dr. King put it, was that he appraised evidence in the light of his theories, which he was incapable of changing.

Our knowledge of the nature of fever, for millennia one of the most important problems for the practicing physician, still remains incomplete. However, it is still progressing as is shown by the recently opened line of attack on the molecular mechanisms evolved in its production. This is indeed a long step from the 18th century views of Boerhaave and his pupils, Van Swieten and Huxham. Pringle's emphasis on the bilious (remitting and intermitting) fevers and those of Cullen, the leading British physician of the century, and his opinionated pupil, John Brown. Cullen's great American pupil, Benjamin Rush, though like the rest chasing wil

theories in the absence of sound basic evidence, showed how frequently, in spite of this handicap, an active and imaginative intellect could inaugurate useful lines of procedure.

In the chapter on homeopathy Dr. King gives a fair and tolerant picture of its author, Samuel Hahnemann—at first an honest scholar but later intolerant and suspicious without common sense, who frequently fell into the *post hoc propter hoc* fallacy, and confused what had happened with what should happen. In spite of the absurdities of increasing potency of drugs with increasing dilution and *similia similibus*, his doctrine still has its followers after more than a century. It was a prime factor, too, in correcting the evils of the polypharmacy of regular medicine in the 19th century.

To the reviewer, an ex-pathologist, with a fondness for medical history, the chapter on the rise of modern pathology, is naturally of especial interest. Novel points of view expressed by the author, himself a pathologist, become all the more striking, as for instance, when he points out that the pathologist, as one trying to understand disease, instead of the clinical concern with symptoms, diagnosis and treatment, was only by chance closely allied to the dissecting table by the early progress of Anatomy. If Chemistry had been the discipline to make the great advances in the 18th and 19th centuries, this pathologist as a student of disease would have been primarily a chemist. It has only been in the present century, that he has tried, or at least seen the logic of, bending any pertinent discipline to his needs. Other divisions of the progressive medical school do likewise with a healthy overlapping of research and correlated teaching.

Many readers of this stimulating work will be most attracted by the final chapter on the practice of medicine, with its case reports, the weird prescriptions written and the account of the rise and fall of inoculation. I must refrain from further comment as I have already overstepped my limit.

It should be unnecessary by now for me to express my approval of this novel collection of historical essays, skilfully welded together to give a cohesive picture of this important period in medical progress. One can more fully appreciate Dr. King's view of the 18th century as the adolescence of present day medicine. He has succeeded in his expressed aim for historical writing, *i. e.*, playing the role of photographer rather than the painter, but recognizing that even as photographer he must choose his material subjectively to get the best results. Finally, the book makes pleasant reading, whether by selecting certain of the essays or more stoutly proceeding from cover to cover.

E. K.

METABOLIC ASPECTS OF TRANSPORT ACROSS CELL MEMBRANES. Edited by Q. R. MURPHY, Madison, Wisconsin. Pp. 374; 134 ills. Madison, Wisconsin: The University of Wisconsin Press, 1957. Price, $7.50.

THIS authoritative book is a symposium dealing with membrane transport. Many aspects of this diverse problem are included. Fields which are summarized are skin, nerve, muscle as well as the mucosae of stomach and intestine. The kidney is also considered. Outstanding contributors represent each discipline. This work can be used to gain a knowledge of basic aspects of membrane transport. It can, in addition, be used to bring those who are already familiar with the fundamental concepts into a closer relation with recent advances in this area.

M. O.

POLYMYOSITIS. By JOHN N. WALTON, M.D., M.R.C.P., First Assistant in Neurology, King's College, University of Durham, in the Royal Victoria Infirmary, Newcastle upon Tyne; and RAYMOND D. ADAMS, M.D., Bullard Professor of Neuropathology, Harvard University. Pp. 270; 47 ills. Baltimore: The Williams & Wilkins Company, 1958. Price, $7.00.

A CRITICAL analysis of various diseases designated generally as polymyositis (dermatomyositis) is presented. The analysis is based on a comprehensive review of the literature and a series of 40 cases observed in this country and in England. Cases of progressive muscular dystrophy and unequivocally infective myositis are excluded. A clear relationship exists clinically between these maladies and other collagen diseases. Alpha$_2$ and gamma globulins are elevated. Photosensitivity is very common. Polymyositis differs from muscular dystrophy electromyographically and by the morphological alterations of the musculature which is characterized by fiber necrosis and phagocytosis followed by regeneration, and by infiltration with plasma cells and lymphocytes followed by fibrosis. The inflammatory changes are so prominent that they can hardly be explained as secondary reaction to primary muscular injury. The authors conclude that polymyositis, dermatomyositis,

"menopausal muscular dystrophy," "late-life muscular dystrophy," "generalized myositis fibrosa," "carcinomatous myopathy" and "interstitial nodular myositis in association with a collagen disease" all appear to be variants of a single syndrome. The cause of the disease is completely obscure. W. E.

KLINISCHE FUNKTIONSDIAGNOSTIK. By PROF. DR. HEINRICH KÜCHMEISTER, Hamburg. II. Medizinische Universitätsklinik & Poliklinik Hamburg-Eppendorf with PROF. DR. W. BOLT, KÖLN; PROF. DR. H. GOLDECK, BREMEN AND DR. H. HAMM, Hamburg. Introduction by PROF. DR. A. JORES, Hamburg. 2nd ed. Pp. 445; 185 ills. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $11.80.

Two editions of this excellent book were printed within two years. The 2nd edition is a thoroughly revised version of the 1st edition. It contains a concise description and interpretation of a rather complete list of function tests of proven clinical value as used in endocrinology, cardiology, hematology, nephrology, gastroenterology and the study of peripheral circulation, respiration, liver, pancreas and metabolism. The book is richly illustrated. It is furnished with 34 pages of references. The authors fully achieved their objective to furnish practicing physicians with a guide in functional diagnosis. W. E.

A TEXTBOOK OF CLINICAL NEUROLOGY. By ISRAEL S. WECHSLER, M.D., Consulting Neurologist, The Mount Sinai Hospital, New York. 8th ed. Pp. 782; 179 ills. Philadelphia and London: W. B. Saunders Co., 1958. Price, $11.00.

THIS is the eighth edition, the first since 1952, of that old reliable textbook on neurology which has nurtured and been the Bible of so many practicing clinical neurologists. The reviewer was, indeed, happy at its appearance. Its author is, of course, one of the deans of the specialty, a man respected and admired by all.

This text, as always, is an excellent one for use by the student. Later he has no difficulty looking things up as he runs into problems in his practice. It has been revised, as required by the changes which 5 years demand. Possibly more emphasis on the physiatric and rehabilitation aspects of neurologic diseases might have been indicated and perhaps more consideration of treatment would have been justified in some instances.

Finally, the reviewer cannot refrain from making a favorable comment on the continued inclusion of chapters on the neurological examination, psychological diagnosis and the neuroses. He feels strongly that these belong in a treatise on neurological diseases. The new edition is again recommended. S. G.

MODERN TRENDS IN ENDOCRINOLOGY. Edited by HAROLD GARDINER-HILL, M.D., F.R.C.P., Consultant Physician to St. Thomas's Hospital, London. Pp. 298; 15 ills. and 1 color plate. New York: Paul B. Hoeber, Inc., 1958. Price, $13.50.

THIS is an extremely valuable book for endocrinologists, internists, and investigators in the biological sciences. It comprises a group of contributions from authorities in the respective fields. Advances which have occurred within the last 10 years are reported and interpreted. It is generally well written and authoritative. W. P.

DIE PHYSIOLOGIE DES LYMPHOZYTENWECHSELS UND SEINE BEEINFLUSSBARKEIT DURCH HORMONE DES HYPOPHYSEN-ADRENAL-SYSTEMS. By H. G. HANSEN, Universitaets-Kinderklinik, Kiel, Germany. Pp. 164; 74 ills., some in color. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $4.40.

THE greater part of this monograph deals with experimental investigations of the lymphatic system and the lymphocyte. From studies of the lymph of the thoracic duct (cat) it is concluded that the number of lymphocytes supplied to the blood stream is adequate to replace the entire lymphocyte content of the blood every 18 hours. Further studies deal with lymphocytes tagged with P_{32} as well as with acridin orange, a basic acridin dye which is bound to the proteins of the cell, especially of the nucleus and permits identification of the tagged cell by means of fluorescence microscopy. One conclusion from these studies is that recirculation of lymphocytes practically does not occur. lymphocytes either enter tissues, or are arrested in lungs, liver and spleen (in that order), there to be destroyed. It appear impossible to raise the level of lymphocytes in the blood by lymphocyte infusion. Experi

ments with ACTH and cortisone, using the method indicated above, lead to the conclusion that the lymphopenia induced by this agent is due to a diminished supply, and probably also to an increased destruction of lymphocytes.

In a short section the application of these results to clinical uses of ACTH and cortisone, especially in leukemias and lymphopathias of childhood is discussed. A rather fascinating though somewhat speculative short chapter deals with possible relationships of the lymphatic system to body growth. There are 452 references. Finally the excellence of print and illustrations should be mentioned.

K. P.

HOST-PARASITE RELATIONSHIP IN LIVING CELLS. A Symposium. Edited by HARRIET M. FELTON, M.D. Pp. 245; 48 ills. and 3 color plates. Springfield, Ill.: Charles C Thomas, 1957. Price, $6.50

A BASICALLY oriented, interdisciplinary approach to the area of host-parasite relationships was undertaken at the first James W. McLaughlin Symposium held at the University of Texas Medical Branch in 1956. The proceedings of that meeting have now been made available to other investigators through publication of this volume. Included are 8 major papers and the discussions which followed them. These dealt with the role of the electron microscope in the study of host cells and of parasites; with cytopathology; and with the competitive aspects of tissue cell and bacterial physiology. In addition, there were considered the morphological basis of the immune response and hypersensitivity; concepts of immunity in virology; metabolic interrelationships between host and parasite; and parasite resistance to host factors.

Microbiologists and cell physiologists will derive much information and stimulation from this volume.

C. Z.

GENERAL PATHOLOGY. Edited by SIR HOWARD FLOREY, Professor of Pathology, Sir William Dunn School of Pathology, University of Oxford. 2nd ed. Pp. 932; 370 ills. Philadelphia and London: W. B. Saunders Co., 1958. Price, $16.00.

THIS book of GENERAL PATHOLOGY is based on lectures delivered at the Sir William Dunn School of Pathology, University of Oxford. There are fifteen contributors, chief among whom is H. W. Florey, who is the recognized author. This is a complete and comprehensive text relative to the basic aspects or basic principles of Pathology in general or of disease in general. There is no discussion of special or specific organ pathology. Five chapters are devoted to inflammation, these chapters are well documented and excellently presented, although a classification of inflammation according to the type or nature of the exudate is only sketchily given and inferred. The next several chapters are concerned with vascular disturbances including edema, thrombosis, embolism and atherosclerosis, and others; these pages cover the subject thoroughly and clearly. The degenerative or retrograde changes are discussed mainly from the standpoint of biochemical changes in the cells, stressing the disturbed or deranged enzyme system; the gross and microscopic features of the infiltrations and degenerations and their clinical significance are only briefly mentioned. There are two chapters on healing which handle this phase of inflammation or of injury adequately. The ensuing chapters proceed in the same vein continuing with general considerations of neoplasms, irradiation effects on tissues, pathogenicity and virulence of microorganisms, and the reaction of cells and tissues to viruses, and others. This is an excellent reference or postgraduate text for the advanced student of medicine, whatsoever his interest or specialty, and for the pathologist in general, who should be familiar with the basic or fundamental aspects of disease, but, who has neglected these aspects for the more colorful and dramatic features of specific disease.

A. P.

THE COLLECTED PAPERS OF HUGH TRUMBLE. Edited by LEONARD COX, M.D., R. S. LAWSON, AND T. E. LOWE, M.D. Pp. 301; 143 ills. Melbourne, Australia: Alfred Hospital, Melbourne, in association with the Melbourne University Press; New York: Cambridge University Press, 1957. Price, $15.00.

THIS volume is a tribute by his associates to Dr. Hugh Trumble who served the Alfred Hospital in Melbourne, Australia, for more than 20 years as honorary surgeon.

Dr. Trumble is versatile. Few surgeons now living have mastered one specialty after another as he has. His contributions to the surgery of the autonomic nervous system have been quoted in standard works of surgery for the last 20 years. His operation for extra-articular arthrodesis of the hip joint has been accepted by Orthopedic surgeons

throughout the world. He became a pioneer in Neurosurgery in Australia and made many outstanding contributions in this field.

This volume contains only selective papers and are grouped under orthopedic surgery, surgery for tuberculosis, surgery of the autonomic system, surgery of intracranial tumors, and the last section is devoted to general surgery.

Although this book may not appeal to the general medical reader, his papers on the autonomic nervous system reveal his original contributions and will be of interest to all doing this type of surgery. His contribution on pituitary tumors is extremely interesting and replete with careful clinical observations.

Dr. Trumble is a skillful surgeon and well deserves this tribute by his associates. This book is recommended to all interested in general surgery and the specialties of Orthopedics and Neurosurgery.

Unfortunately, the high price of this book will limit the circulation it deserves. M. S.

Clinical Cardiopulmonary Physiology. Edited by Burgess L. Gordon, M.D., Woman's Medical College of Pennsylvania. Pp. 740; 248 ills. New York: Grune & Stratton, Inc., 1957. Price, $15.75.

This useful text has an authoritative Editorial Board. To the expanding numbers of workers in the cardiopulmonary field this book should be a source of guiding material for those just entering the discipline and for those who are already conversant with its ramifications. All the sections are good although some are considerably stronger than others.

The division of Examination and Testing is most useful. While intimate details of procedures are not always given the explanations are lucid and interpretations clear. Illustrations are numerous and informative. The section on Acquired Valvular Heart Disease; Clinical and Hemodynamic Features, is particularly to be recommended. M. O.

Les Principes de L'Electrophorese. By Rene Audubert and Serge de Mende, The Sorbonne. Pp. 201; 102 ills. Paris: Presses Universitaires de France, 1957.

Paper electrophoresis is being utilized as a diagnostic tool in an increasing number of clinical laboratories as well as by research workers. The present authors have recognized many of the pitfalls which occur by widespread use of a research tool when its theoretical aspects are not understood. They are to be commended for setting down many of the basic phenomena concerned and for pointing out the dangers involved in applying empirical procedures to substances of unknown composition. They cite not only their own experiences, but those of a large number of others, especially the European workers. The book is replete with diagrams and photographs. It should be of great value to those who contemplate using this tool. Although the paper binding does keep down the cost, one might wish for a more permanent type of binding on such a useful book. R. B.

Les Facteurs de la Croissance Cellulaire. Activation et Inhibition. Publiés sous La Direction de J. André Thomas, Professor of Cellular Biology at the Sorbonne, Paris, France. Pp. 428; 65 ills. Paris: Masson et Cie, 1956. Price, 4000 fr.

This is a very ambitious undertaking in which a number of well-known investigators have contributed to the important topic of cellular growth and inhibition. The monograph starts with a most interesting survey by J. Brachet of the activating and retarding factors involved in the synthesis of proteins. Much of the content of this chapter has originated in the author's own laboratory. For instance, Brachet indicates the important role played by ribonuclease in inhibiting protein synthesis, whereas the synthetic processes seem to be referable to a combination of ATP produced by mitochondria and nucleic acid, particularly RNA.

In another chapter, K. V. Thimann and P. Chouard analyze the factors concerned in cell growth in plants. The discussion centers around the role of auxins in plant growth. The auxins *per se* do not appear to react singly but rather as an important complementary factor to other factors involved in this complex process. Physiological embryology is considered at length in a chapter by Etienne Wolff. This author describes the methods of growing *in vitro* embryonic organs. He points out the necessity of SH derivatives, particularly cysteine, the predominating role of arginine, and the efficiency to growth brought about by some amino acids, notably histidine, lysine, glutamic acid, and the addition of ornithine, threonine, asparagine, and hydroxyproline. With various tissues certain changes become indispensable, *e.g.* folic acid for some explants. M. P. Dustin considers very thoroughly the factors concerned in mitotic inhi

bition of animal cells. This investigator points out the importance of mitotic inhibition as a tool in the study of mitosis by demonstrating the various cellular derangements or lesions that may develop under special circumstances. The study of chromosomal poisons have permitted the study of differences in normal and neoplastic tissues. The importance of the study of mito-inhibitory factors in plant cells is considered by Guy Devsson who arrives at the conclusion that such studies on plant cells may have wide applications and repercussions in general biology; and may yet prove to have application even in problems of human pathology and therapeutics.

This interesting book concludes with a consideration of the factors involved in cancer growth. The author is Ch. Oberling, a well known proponent of the virus etiology of cancer. Oberling admits the possibility that viruses as other cancerinogenic agent act on chromosomal structures which in turn determine irreversible modifications leading eventually to cancer. In other words, the virus would initiate a chromosomal disease which subsequently can evolve even in the absence or with the loss of the virus into a true cancer. However, according to Oberling one can also envisage that the nucleo-protein in the virus itself may act as a foreign gene which in turn can convey autonomy to the cell leading to neoplastic formation.

This book is highly recommended to the investigator of both cell physiology and cellular pathology. V. M.

The Appraisal of Applicants to Medical Schools. Report of the Fourth Teaching Institute, Association of American Medical Colleges, Colorado Springs, Colorado. November 7–10, 1955. Edited by Helen Hofer Gee and John T. Cowles. Pp. 228; illustrated. Evanston, Ill.: Association of American Medical Colleges. 1957. Price, $3.00, cloth; $2.00, paper.

This publication is the report of the Fourth Teaching Institute of the Association of American Medical Colleges. The subject for consideration at this institute was the evaluation of the student applying to medical school. A great deal of investigation had been done prior to the institute, and each of the factors was considered critically in small discussion groups. This book represents a report on some of the findings and some of the conclusions reached. Psychologists, sociologists and anthropologists have cooperated with medical educators to a very great advantage. The entire process of the selection of medical students and the admissions procedures are investigated. As one would expect, there are no distinct answers, but there is a tremendous amount of material which would be of interest to all those engaged in medical education. This book is recommended as a must for medical educators who did not attend the conference and is highly recommended to all those in the medical, and related fields, who have to do with the growth of the profession. R. B.

Theory and Problems of Child Development. By David P. Ausubel, M.D., Ph.D., Bureau of Educational Research, University of Illinois. Pp. 650. New York: Grune & Stratton, Inc., 1958. Price, $12.00.

In the Preface the author states that this book is an outgrowth of his conviction that the time is presently ripe for some systematic stock-taking in theory and problems of child development. He should find much support of this conviction.

This text represents an admirable effort on the part of the author to present his own views on the present status of the field of study known as child development, and in addition, will serve as an excellent reference source to all interested in this field.

The author's tendency to use lengthy, involved sentences makes the first section of the book difficult to read. The more factual material, however, of the later sections is written in a more lucid manner.

The author appears to have succeeded to an extent in bringing into a more precise perspective the huge amount of material which has accumulated in the study of child development. R. O.

Shock and Circulatory Homeostasis. Transactions of the Fifth Conference, November 30, December 1 and 2, 1955. Edited By Harold D. Green, M.D., Professor of Physiology and Pharmacology and Associate in Internal Medicine, Bowman Gray School of Medicine, Wake Forest College. Pp. 337; 78 ills. New York: The Josiah Macy, Jr. Foundation, 1957. Price, $4.75.

This book represents the transactions of the fifth conference on experimental work in shock. The organization of the volume is similar to the publications on the previous transactions. Various experiments are described, and group discussion is related so that the

reader has the benefit of critical analysis and of comparison, which he would not obtain from a monograph written by the author of the experiment.

Several very important aspects of experimental shock are considered. The first is "Hepatic Blood Flow in Experimental Shock" by Stanley E. Bradley. "The Bacterial Factor in Experimental Shock" is then considered, and the first paper is by Jacob Fine. Silvio Baez next presents work done to demonstrate the mechanism of the protection afforded by aureomycin against shock. This would question the theory that aureomycin is used only as an antibiotic. A very interesting group of experiments is then described by Benjamin W. Zweifach, in which experimental shock was studied in germ-free rats. The remaining conferences deal with the effects of blocking agents, humoral factors, and hypothermia in experimental shock.

Once again, this book is recommended to all those interested in the experimental aspects of shock, as it presents the material in a way which other publications do not. R. B.

Die Lungenarterienbahn bei Angeborenen Herzfehlern. By Priv.-Doz. Dr. Med. Kurt Kühn and Dr. Med. Marianne Richter, Department of Pathology, Free University of Berlin. Pp. 112; 52 ills. Stuttgart: George Thieme Verlag, 1958 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $7.00.

This anatomic-pathologic study was carried out for 41 cases of congenital cardiovascular malformations. In each instance the available clinical data are given. The findings were plotted against types that reveal either (Group I) increased pulmonary artery filling (with or without pulmonary artery hypertension), patent ductus arteriosus, interventricular septal defect, interatrial septal defect, pulmonary vein transposition, Eisenmenger and Taussig-Bing syndrome, or (Group II) diminished pulmonary artery filling (with pulmonary hypotension), Fallot and Ebstein syndrome, or (Group III) where the blood volume is about equal in the greater and lesser circulation, aortic stenosis and coarctation of the aorta. The changes observed in the pulmonary arteries are described in three categories: A) Alterations chiefly in the great and middle-sized vessels, B) alterations that particularly affect the small arteries, arterioles, and precapillaries, and C) the occurrence of thin endothelial septa and hemangioma-like formations, considered to be congenital anomalies. There are 491 references pertaining to the German, Anglo-American, French and Italian literature. Illustrations and print are of the highest type. H. R.

Orthopedics for the General Practitioner. By William E. Kenney, M.D., and Carroll B. Larson, M.D. Pp. 413, 180 ills. St. Louis: C. V. Mosby Co., 1957. Price, $11.50.

The text, by the authors' definition, is a reference book for the entire field of orthopedic surgery and accomplishes its task satisfactorily. The illustrations are clear with but few exceptions and enhance the reading matter quite satisfactorily.

The authors trust that "this book will be primarily helpful to the family doctor treating the orthopedic problem encountered." One wonders if it should not serve, as it does admirably, to clarify the pitfalls of missed diagnosis rather than point out treatment methods which almost invariably come within the realm of the orthopedic surgeon. Many arguments on treatment would have to deal with methodology but basically the therapeutic approach is conservative. One would have to quarrel with the lack of adequate bibliography particularly in areas where the interests of the general practitioner might be aroused by the material outlined in the text. The repetition of subject matter may also be a fault but this could scarcely be prevented with the organization of the book along the lines of regional anatomy and in age groups.

I would question the value of the textbook to the orthopedic surgeon but feel it might be helpful to the medical student and also to the general practitioner by outlining the broad field of orthopedics and particularly in making clear the areas where diagnostic error can lead to serious consequences.

H. S.

Sherrington: Physiologist, Philosopher and Poet. By Lord Cohen of Birkenhead, M.D., D.Sc., LL.D., F.R.C.P., F.A.C.P., F.F.R., F.S.A., J.P., Professor of Medicine, University of Liverpool. The 4th Sherrington Lectures, University of Liverpool. Pp. 119; 3 portraits and 17 figs. Liverpool: Liverpool University Press, and Springfield, Ill.: Charles C Thomas, 1958. Price, 17s. 6d.

This series, given by the well-known Professor of Medicine at Liverpool, in its three lectures treats of Sir Charles Sherrington.

O.M., G.B.E., F.R.S. (1857–1952) as the man, the physiologist, the philosopher and poet. The lecturer's brief sketch of Sherrington's life is interlarded copiously with the evidence of his physiological development. He was interested in the nervous system from his student days, with but few medical interruptions such as a visit to a cholera epidemic in Spain, where he began his lifelong friendship with Golgi. His connection with the cerebral localization problem produced (1884) his first paper, which eventually numbered over 320. His work at Liverpool on reflex action and reciprocal innervation paved the way for his Silliman Lectures at Yale (1904, published 1906) on "The Integrative Action of the Nervous System," a work that has been ranked in importance by one enthusiast with Harvey's "De Motu Cordis," "for it marked a turning point in the history of physiological thought." Throughout his career, his physiological investigations resulted in publications that fill 37 pages of a Bibliography, a feature that alone earns a place for this book in any scientific library. His last entry in Who's Who (1952) shows how warmly he was appreciated throughout the world, receiving 22 honorary degrees and 28 honorary memberships, as well as many positions of distinction.

In the third lecture on the philosopher and poet, one continues to learn so much about this great figure. Though his laboratory researches pursued only the how of life, he was always interested in the why, which he wisely regarded as not in the province of physiology. He was free to pursue it, however, after his retirement, perhaps on the theory that it is better to travel than to arrive. In the short five pages devoted to Sherrington as a poet enough is revealed—sonnets and lyrics—collected poems published 30 years ago—to lead one to agree that his deepest emotions found outlet in poetic thought and writing. In fact, as one who was acquainted with him but slightly, I find little to disagree with in the lecturer's estimate of him as one "who had been the world's foremost biologist, a deep thinker, philosopher and poet, a genius of rare human qualities—humility, modesty, kindness, sincerity, toleration, graciousness, and a lover of all things beautiful." E. K.

Histologie der Hautkrankheiten. By Oscar Gans and Gerd-Klaus Steigleder. Universitat Frankfurt a.M. 2nd ed. Vol. II. Pp. 706; 290 ills., many in color. Berlin: Springer Verlag, 1957. Price, DM 298, for set.

The first volume of this work was reviewed in April, 1956, (**231**, 483). The second volume continues in the same high plane of presentation. It covers well-indexed discussion of the reactive processes (dermatitides); the mycoses of the skin; animal parasites and foreign bodies; circulatory disturbances; developmental abnormalities and true tumors. The range of individual topics covered in the 706 pages of this book is comprehensive and is hardly indicated by the major subdivisions listed above. Histologie der Hautkrankheiten is an important contribution to the dermatologic literature.

H. B.

Die Neuzeitlichen Brustwand- und Extremitäten-Ableitungen in der Praxis. By Prof. Dr. Herbert Reindell and Doz. Dr. Helmut Klepzig, University of Freiburg, West Germany. 3rd ed. Pp. 192; 82 ills. Stuttgart: G. Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $7.00.

This is an up-to-date presentation, based upon studies of the authors and of the international literature. Particularly good are the statistical data of what comprises the range of normal, the discussion of delayed excitation and the chapters on myocardial infarction. In several cases there is a valuable correlation with postmortem data. A serial case report on the effect of meals on the electrocardiogram, and the correction by using KCl is instructive. Vectorcardiography is mentioned insofar as it will lead to a better understanding of the regular electrocardiogram. The make-up of this monograph is of a high type. H. R.

Medical Jurisprudence and Toxicology. By John Glaister, J.R., D.Sc., M.D., F.R.S.E., F.R.F.P.S., and Edgar Rentoul, M.B.E., M.A., LL.B., M.B., Ch.B.; Regius Professor of Forensic Medicine and Lecturer in Forensic Medicine, University of Glasgow, respectively. 10th ed. Pp. 720; 275 ills., 72 in color. Baltimore: The Williams & Wilkins Company, 1957. Price, $10.00.

This is a comprehensive text on medicolegal problems and on toxicological agents. The introductory chapter defines Medical Jurisprudence, refers to various Medical Acts, includes roughly two pages on Malpraxis and

concludes with Legal Criminal Procedures in England and in Scotland. The ensuing chapters deal with medical evidence, identification of living and dead persons, signs of death and changes following death, asphyxia, rape, and others. The text is well illustrated throughout by pictures and by pertinent case histories, thus demonstrating the wide experience of the authors. The last 11 chapters deal with poisons, their symptoms, treatment and postmortem features. Chemical tests for the various poisons, arranged alphabetically, make up Appendix II. This is a well written book and contains a wealth of information for the medical examiner's or coroner's group and for those concerned with medicolegal problems. In addition, it affords extremely interesting reading for the medical and nonmedical man, who has little or no contact with forensic medicine, but who is intrigued by medicolegal cases and their solutions.

A. P.

A Manual of Electrotherapy. By Arthur L. Watkins, M.D. Massachusettes General Hospital. Pp. 259; 167 lils., 1 plate in color. Philadelphia: Lea & Febiger, 1958. Price, $5:00.

This manual, intended for use by therapists, medical students and physicians, presents the subjects of Electrotherapy and Electrodiagnosis. It covers physical therapy procedures where the basic form of energy employed is electrical and includes the subjects of infra red, ultraviolet, low frequency currents, diathermy and ultrasound.

The author retains the style and many illustrations of the late Doctor Richard Kovacs whose books have been popular with students in the field for many years.

The discussion of electromyography is so brief that it tends to belittle its growing importance in the field of diagnosis.

All in all this book covers the realm of electrotherapy in a clear, concise and adequate fashion.

E. S.

Pharmacology in Medicine. Edited by Victor A. Drill, Ph.D., M.D., Northwestern University Medical School, University Illinois College of Medicine, and G. D. Searle & Co. 2nd ed. Pp. 1243; 205 ills. New York: McGraw-Hill Book Co., Inc., 1958. Price, $19.50.

This volume is a collaborative textbook. The special qualifications of the 86 contributors and their reputations as investigators and teachers are impressive. Despite the number of contributors the text displays a degree of continuity often lacking in such collaborative works. The book is well organized and is subdivided into 19 parts, arranged insofar as possible according to the major systems of the body. The first chapter provides a brief but valuable discussion of historical background and general principles which is very helpful in providing orientation in this field. Several changes have been instituted since the first edition and are, in the opinion of this reviewer, distinct improvements: pages are numbered consecutively throughout the book, an addendum has been added by which it is planned to keep the book up-to-date in subsequent printings, and a part has been added on "Psychopharmacology." The book is again well illustrated and is adequately documented by selected references. The volume is large but very readable, and both students and teachers would profit from reading it. It can also serve as a sound and valuable reference source for practicing physicians in these times of rapid expansion in the field of drug therapy.

R. S.

Psychotherapy by Reciprocal Inhibition. By Joseph Wolpe, M.D., Lecturer in Department of Psychiatry, University of Witwatersrand, South Africa. Pp. 239; 5 ills. Stanford, California: Stanford University Press, 1958. Price, $5.00.

Neurotic behavior originates in learning; and cure of the neurosis is a matter of unlearning. Drawing heavily from Pavlov and Hull, the author presents a theory to explain how a habit can be overcome by forming a new and antagonistic habit in the same stimulus situation. Wolpe asserts that by deliberately applying responses, neurotic anxiety-response habits can be overcome.

According to the author, whatever good results are obtained through psychoanalysis and other forms of psychotherapy are achieved through the reciprocal inhibition principle without the therapist realizing it.

A case is described of a man pathologically attracted to buxom women. The symptom originated from a childhood interest in the mother's sister. Naively oblivious to oedipal problems, Dr. Wolpe nevertheless achieves a cure by encouraging his patient to assert himself with people and to speak up against the wife continuing her affair with another man.

The author claims that 90% of his patients

are cured or much improved with his new therapy. M. B.

5-Hydroxytryptamine. Edited by G. P. Lewis, Ph.D., National Institute for Medical Research, Mill Hill, London. Pp. 253; 67 ills. New York: Pergamon Press, 1958. Price, $9.50.

This volume contains the proceedings of an international symposium. The subject, 5-Hydroxytryptamine (serotonin) could hardly be more timely in view of the marked and widespread interest in, and speculations about the functions of, this interesting compound. This book is by no means an answer to all questions raised regarding 5-Hydroxytryptamine, especially to the question of its functions. However, it does bring together the investigations and views of 47 qualified participants from many parts of the world. Topics discussed are: occurrence and metabolism, peripheral actions, and central actions of 5-Hydroxytryptamine. Within the sections on peripheral actions are included discussions of the relation of 5-Hydroxytryptamine to carcinoids, and to the phenomenon of anaphylaxis, and peripheral antagonists of 5-Hydroxytryptamine. A discussion of central antagonists is included in the section on central actions. The book is both informative and stimulating. R. S.

Der Lungenboeck im Röntgenbild. By Prof. Dr. K. Wurm, Prof. Dr. H. Reindell and Prof. Dr. Dr. h.c.L. Heilmeyer. Pp. 220; 180 ills. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $18.55.

This is a Roentgen atlas that includes a description and discussion of clinical findings, pathology, prognosis, and treatment. The intrathoracic localization of this generalized epitheloid cell granulomatosis was first time described by Schaumann in 1914. The material comprises more than 300 cases, with many of them followed over several years. The thoracic manifestation of the disease (mediastinum and lungs) is presented for its three different stages in pathogenesis and radiologic appearance, with remarks as to sequential developments, duration of the disease, reversibility and outcome. Special features stressed are: the relationship between mediastinal lymphnode and pulmonary involvement, respectively; the effect of cortisone; and the temporarily, beneficial effect of pregnancy. The case reports, in addition to radiologic illustrations, give pertinent clinical and laboratory data. Differential diagnosis is discussed with respect to a) mediastinal localization: inflammation, Hodgkin, leukemia, primary and metastatic tumors and to b) pulmonary localization: tuberculosis, syphilis, toxoplasmosis, mycosis, silicosis, fibrosis, lymphogranulomatosis and malignant tumors. H. R.

Psychopathology of Communication. Edited by Paul H. Hoch, M.D., New York State Psychiatric Institute; and Joseph Zubin, Ph.D., New York State Psychiatric Institute. Pp. 305; 7 ills. New York and London: Grune & Stratton, Inc., 1958. Price, $6.75.

Seventeen papers by different authors are brought together in this volume to further elucidate the problem of communication. Social scientists have given considerable attention to communication for the past decade and more recently the psychopathologist has become interested in this problem.

This volume points the way toward scientific evaluation of the interview as a communicative act. A better understanding of communication will be helpful in gaining a deeper understanding of the private experiences of the patient. Unfortunately, there is a trend toward over-emphasizing the significance of communication at the risk of underestimating the forces within the organism that control behavior.

This volume is expressive of a new school of thought that can offer the psychopathologist another tool in his work. This reviewer gains the impression, however, that there is a tendency toward exaggerating its significance and disturbed communication is being viewed as the cause rather than the result of psychopathology. M. B.

No and Yes (On the Genesis of Human Communication). By René A. Spitz, M.D. Pp. 170. New York: International Universities Press, Inc., 1957. Price, $4.00.

Dr. Spitz, well known for his original studies of the psychological development of infants, devotes this monograph to the study of preverbal communication. He investigates communication phenomena occurring before the use of words. Although negative caphalogyric motions might be a meaningful behavior in terms of a particular personality, Spitz assumes this behavior is connected to a pattern which was present at an earlier developmental stage.

The author investigates the preformed behavior

patterns which have a function in the earliest nursing situation. Two phenomenologically similar movements, the semantic signal of "No" and rooting behavior, have diametrically opposite significance. The former communicates a refusal, while the latter represents a striving toward.

Spitz uses Freudian psychoanalysis as his frame of reference for his investigations. The book should be of value to all interested in human behavior and in the inter-reactions of people.

M. B.

Juvenile Epilepsy. Report of a Study Group of the World Health Organization. Pp. 44; 1 ill. Geneva: World Health Organization, 1957. Price, $.30.

This is the report of a study group assigned to accumulate available information on various aspects of epilepsy such as prevalence, etiology, clinical, social and psychologic patterns, case finding, treatment and public health factors.

W. N.

Anaesthesia. British Medical Bulletin, 14, No. 1. January, 1958. Pp. 72; illustrated. London: Medical Department of The British Council, 1958. Price, 20 s.

A Primer for Coronary Patients. By Robert J. Needles, M.D., and Edith M. Stoney. Pp. 176; 22 ills. New York: Appleton-Century-Crofts, Inc., 1958. Price, $3.75.

This is a delightful book about coronary artery disease, what it is, what it does, what can be done about it and how a productive life may be continued in spite of it. There is also a discussion of the nature and origin of cardiac symptoms not due to cardiac disease and what a person should expect when he goes to a doctor because of his heart. Finally, common queries are given and answered. It is as much a handbook for those with coronary artery disease as Joslin's is for diabetics. Although written especially for persons with coronary artery disease, it may be read profitably by the public at large and by physicians too.

J. Z.

Biochemical Preparations, Volume 5. Edited by David Shemin, College of Physicians and Surgeons, Columbia University. Pp. 106. New York: John Wiley & Sons, Inc., 1957. Price, $4.75.

The excellence of this series of publications is maintained in Volume 5. This is undoubtedly due in great degree to the judgment of the advisory and editorial boards, many of whom serve as editors of the Journal of Biological Chemistry.

The preparations described in this volume include enzymes, coenzymes, metabolites and intermediate compounds which run the gamut in biological interest. Directions are given for the preparation of 25 important compounds and for the separation of both RNA and DNA nucleotides.

R. B.

The Medical and Veterinary Importance of Cockroaches. By Louis M. Roth and Edwin R. Willis, Pioneering Research Division, Quartermaster Research and Engineering Center, Natick, Mass. Pp. 147; 7 ills. Washington: Smithsonian Institution, 1957.

In this excellent monograph on the Medical and Veterinary Importance of Cockroaches, Roth and Willis have carefully reviewed and summarized the available literature in reference to the known relationships of cockroaches and the organisms that cause disease in man and animals. The cockroach has generally been considered more of a nuisance than as a potential transmitter of disease. In this review of the literature the disease transmission potential is markedly brought into focus. These insects have long been incriminated as mechanical vectors in the transmission of protozoan cysts and helminthic ova and in a few cases are actual intermediate hosts of nematode parasites. In the excellent appendices the authors summarize the pathogenic viruses, bacteria, fungi, protozoa and helminths that are naturally or experimentally associated with these insects. Cockroaches may play a very important role as potential mechanical vectors in the dissemination of infectious agents.

E. S.

Naturally Occurring Quinones. By R. H. Thomson, D.Sc., Ph.D., F.R.I.C., University of Aberdeen. Pp. 290. New York: Academic Press, Inc.; London: Butterworth Scientific Publications, 1957. Price, $9.00.

One of a series of "Organic Chemistry Monographs," Dr. Thomson's book provides a rather comprehensive review of the chemistry and occurrence in nature of selected benzoquinones, naphthaquinones, anthraquinones, phenanthraquinones and "extended" quinones.

The book should be of interest to workers in the fields of phytology, mycology and zoology and especially to individuals concerned with the chemistry of natural products.

In addition to a general index there is a zoological and a botanical index of organisms and plants referred to in the text.

The monograph is well documented; a total of over 900 references are cited. Over 700 structural formulas are appropriately spaced throughout the textual material.

R. B.

The Neuroses and Their Treatment. Edited by Edward Podolsky, M.D., in collaboration with Siegfried Fischer, Montague Ullman, Frank C. Metzger, Max M. Stern, Henry H. Brewster, Paul Chodoff and L. J. Meduna. Pp. 55[illegible] New York: Philosophical Library, Inc., 1958. Price, $10.00.

This book collects the writings of some fou[illegible] authors from fifteen different journals. There [illegible] papers regarding anxiety in infancy and chil[illegible] hood and three papers on hysteria in childhoo[illegible]

also papers on the occupational neuroses; the neuroses of everyday living, compulsion neurosis, phobic reactions, neuroses of the middle-aged man and psychosomatic reactions. Treatment in psychiatry is represented by writings regarding psychotherapy, the administration of chlorpromazine, sedatives, carbon dioxide, lobotomy, meprobamate, nassurance, and abreaction. Several papers regarding research are also included. No particular thesis is developed nor is there a clear relationship between the various presentations.

M. B.

The Essence of Surgery. By C. Stuart Welch, M.S., M.D., Ph.D., Professor of Surgery, and Samuel R. Powers, Jr., A.B., M.D., M.Sc.D., Professor of Experimental Surgery, Albany Medical College. Pp. 320; 50 ills. Philadelphia: W. B. Saunders Co., 1958. Price, $7.00.

"The Essence of Surgery" is aptly titled and is a concise and clear presentation of the basic principles of surgery. The authors are to be complimented on the excellence of the work. In some respects the text is a little advanced for medical students but is ideally suited for the surgical resident.

R. T.

Eksperimentelle Undersøgelser Over Thyroxins Induirkning På Helende Sår. With a Summary in English. By Erik Moltke. Pp. 46; 9 ills. Copenhagen: Ejnar Munksgaards Forlag, 1958. Price, Da Cr. 7.50.

Heart Disease: Cause, Prevention and Recovery. By Philip S. Chen, Ph.D., Professor and Chairman of Division of Natural Sciences, Atlantic Union College, with the assistance in Part I of Philip S. Chen, Jr., Ph.D., National Heart Institute. Pp. 189; 14 ills. South Lancaster, Massachusetts: Chemical Elements, 1958. Price, $3.00.

This book was written to acquaint the layman with "the whole subject of heart disease according to the most recent discoveries made in the fields of medicine, biochemistry and nutrition." Actually, the book is devoted almost exclusively to coronary atherosclerosis. This disease today is regarded by the most vocal students as a metabolic disturbance due to excessive consumption of saturated fatty acids.

The author, who is a biochemist, marshals strong evidence to convince the reader of the correctness of this hypothesis. The scientific reader may be agitated by biblical quotations and references to religious sects used as additional support. The book ends with a prediction of future dietary habits which will abolish atherosclerosis.

This unilateral approach to the problem ignores other possible factors such as hypertension and the all important relation between atherosclerosis and thrombosis. But so do many physicians.

More important is whether such a book, regardless of the correctness of the hypothesis, is good or bad or ineffective for those persons who are attracted by or seek such titles. The reviewer is unfamiliar with any scientific study of this sort.

L. S.

Diabetes as a Way of Life. By T. S. Danowski, M.D., Renziehausen Professor of Research Medicine, University of Pittsburgh School of Medicine. Pp. 177; 27 ills. New York: Coward-McCann, Inc., 1957. Price, $3.50.

This guide for diabetic patients contains much practical information for their self-care. The material is presented in an attractive and readily comprehensible style. The contents cover the important details of dietary management utilizing the food exchange system and provides a thorough discussion of insulin therapy. The methods employed by the author are not always those recommended in other clinics but nevertheless are widely used in the care of diabetes. For example, the sterilization of the syringe by boiling rather than by alcohol or Zepharin is not always advised; under the section on surgery, the reversion to regular insulin during operation advocated by the author is not practiced in all centers. The final chapter dealing with the diabetic life and its impact upon the individual and his family should be read by all those involved with this disease. A glossary of terms for the diabetic patient and a useful appendix containing detailed material on various subjects conclude this unique and informative manual.

C. S.

Chronicle of the World Health Organization, Vol. 11, No. 10, October, 1957. Pp. 35; 6 ills. Geneva: World Health Organization, 1957. Price, $.30.

Medical Specialization: A Survey of Existing Legislation. Pp. 40. Geneva: World Health Organization, 1958. Price, $.30.

In about 20 countries the requirements for specialists' training are established by law, while in others they have been set up by national medial associations. The purpose of this study is to bring out the trends in legislation and to examine the local requirements for the recognition of specialists.

R. K.

Dreams in Folklore. By Sigmund Freud and D. E. Oppenheim. English translation by A. M. O. Richards under the editorship of James Strachey. Pp. 111; 2 ills. New York: International Universities Press, Inc., 1958. Price, $3.00.

Between the years 1909 and 1911 Professor David Ernst Oppenheim and Sigmund Freud collaborated in a study of the relationship between folklore and psychoanalysis. Oppenheim collected the raw material and Freud arranged

it in an appropriate sequence, adding his interpretations and commentaries. In addition to the English translation, the German version of the manuscript is printed exactly as originally written by Freud.

The fact is established in this book that folklore interprets dream symbols in the same way as psychoanalysis. The common people recognize that dreams represent the fulfillment of wishes, and the satisfaction of needs arising during the state of sleep.

This short work of Freud, published for the first time, is unusually interesting to read.

M. B.

Human Infertility. By C. Lee Buxton, M.D., Med.Sc.D., Professor of Obstetrics and Gynecology, Yale University School of Medicine, Anna L. Southam, M.D., Assistant Professor of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University and Earl T. Engle, Ph.D., Columbia University. Pp. 229; 43 ills. New York: Paul B. Hoeber, Inc., 1958. Price, $7.50.

This book presents, in simple fashion, methods of infertility investigation. Well-established diagnostic methods are described, which will make this book useful to the beginner. It seems, to this reviewer, that there is undue emphasis on the psychosomatic aspects of infertility although, perhaps, this emphasis is justified in view of the lack of recognition of this important component in the production of infertility.

W. P.

Medicine and Man: The Story of the Art and Science of Healing. By Ritchie Calder. Pp. 256; New York: The New American Library, 1958. Paperback Mentor original. Price, $.50. (Available in cloth binding from George Allen & Unwin Ltd., London.)

This book, a concise history of the evolution of the healing arts, gives a vivid account of man's unending quest for health and longevity. It presents in readable style a popular narrative suggestive of Dr. Victor Robinson's *Story of Medicine*, which was last issued 15 years ago.

Mr. Ritchie Calder, Science Editor of the "London News Chronicle," has written an engaging story of medical progress, from witch doctor to atomic scientist. A nontechnical volume, *Medicine and Man* will be read with interest by doctor and patient alike.

F. B.

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